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Published, in English, in every August and February
Turkish translations of the titles and abstracts are available.

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e-ISSN: 2149-0120
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Copper Octoate: A Commercially Available and Cost-Effective Homogeneous Catalyst for the Facile Synthesis of 2,2’-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones)

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Abstract: A practical and convenient approach for the synthesis of 2,2’-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones) was presented using copper octoate as a homogeneous catalyst. Copper octoate as an eco-friendly, low cost, and commercially available catalyst, reduced reaction times effectively to (16-50 min) while the reaction profiles were absolutely clean and no side products including dehydrated xanthene heterocycle were detected. Pure target compounds were obtained in very good to excellent yields (83-91%) via straightforward work-up procedure. The catalyst was recycled in the form of solution, up to four times, with no noticeable drop in activity.


Keywords: Copper octoate, copper(II) 2-ethylhexanoate, homogeneous catalyst, arylmethylenebis(3-hydroxy-2-cyclohexene-1-one).

Introduction

Application of transition metals as catalysts in organic reactions has achieved widespread acceptance within the synthetic organic community. The gradual realization that complexes of transition metals have a place in synthetic procedures has caused a quiet revolution. Today, there are very rare complex total syntheses that do not involve at least a few transition metal-mediated reactions as key steps. In fact, highly reactive and normally unavailable reaction intermediates can be generated by applying transition metal complexes, and be used as reagents in organic synthesis. Performing some of the metal-catalyzed organic reactions in relatively large scales shows that the aforementioned methods are more than just academic interest [1, 2].

Copper(II) 2-ethylhexanoate (Cu(EH)₂), or copper octoate (Figure 1), is a well-known industrial reagent. It has been used as a preservative in wood industry for several years [3] and is also applied for the preparation of superconductors [4-6]. Because of its long-lasting effect in protection against termites and other insects, it is usually applied in bottom paints of ships. In addition, copper octoate is utilized as rot-proofing agent in textiles and may be applied on textile fabrics by dipping or spraying. Moreover, as a fungicide and bactericide, it has found various applications in household and agricultural products to control a considerable range of plant diseases. Copper octoate has also been used as a catalyst in many organic transformations such as polymerizations [7], preparation of allylic alcohols, and alpha, beta-unsaturated carbonyl compounds from the rearrangement of epoxides [8], aldol reaction [9],...
oxidative coupling of indoles or pyrroles with enolates [10, 11] and oxidative coupling of esters or ketones with amides [12]. There is also a report of utilizing copper octoate as an ignition temperature-depressing agent which is applied as an additive to the fuel supply to promote oxidation of collected soot extracted from the exhaust gas of the engine [13]. An industrial example of using copper octoate as catalyst is its common application as a paint drier. Hydrocarbon chains help absorption of oxygen from the air and copper, on the other hand, acts as a catalyst to speed up the formation of the oxidative coating [14].

![Copper octoate](image)

**Figure 1.** Copper octoate.

Copper octoate and many other metal complexes of 2-ethylhexanoic acid are often described as salts, while, indeed, they are not ionic but charge-neutral coordination complexes. The structure of copper octoate, both in crystalline [15] and solution [16] state, has been investigated. Low polarity and ionic character of copper octoate in addition to its long hydrocarbon chains are the major reasons for the high solubility of copper octoate in organic solvents like xylene and oils, which play a major role in finding extensive and novel applications both in industry and academia [17]. For instance, oxidative intramolecular cyclization of alkenyl amides was carried out successfully in the presence of copper octoate while its acetate salt did not perform well. It was mentioned as a reason that copper octoate has both the comparable activity with copper acetate and a high solubility in the reaction medium which causes homogeneity in the reaction medium [18]. Indeed, combining less toxicity and non-corrosive nature of solid acids and the motility of liquid acids, is the uniqueness of this Lewis acid which makes it a promising catalyst in the field of organic synthesis. Copper octoate is commercially available with quite low costs and in the form of solvated in organic solvents in various grades and with different metal content and solvents which can be manufactured upon customer’s demand.

Arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) derivatives belong to the family of tetraketones which are used as valuable intermediates for the synthesis of various heterocycles such as acidines, xanthenes, and thiaxanthenes which contain structures including dihydropyridine, pyran, and thiapyran [19]. These compounds have applications in laser technology [20] as well as clinical uses as antioxidant [21], tyrosinase [22], and lipoxygenase [21] inhibitors.

The first report about the synthesis and characterization of this class of compounds was by George Merling and in the course of preparing 1,3-cyclohexanedione from resorcinol [23]. Nevertheless, the principle synthetic avenue to arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones) comprises the condensation of an aldehyde with a two-fold excess of 1,3-cyclohexanediol derivatives. This reaction was utilized for identification and characterization of aldehydes and was carried out in aqueous ethanolic solution catalyzed by piperidine [24].

So far, various reaction conditions have been presented for this reaction including, CaCl₂ in chloroform [25], palladium nanoparticles in water [26], urea in water under ultrasonic irradiation [27], FeCl₃·6H₂O and TMSCl in [bmim][BF₄] [28], I₂ in water [29] and ethylenediamine diacetate in THF [30]. Regarding practical, environmental and economic aspects, most of these methods may not be appropriate for industrial applications.
There are also some catalyst-free approaches using water [31], dichloromethane [32] or DMF [33] as solvents and grinding technique [34]. However, long reaction times associated with these catalyst-free reactions, sometimes up to 24 or 48 hours, remarks the necessity of using a catalyst for this reaction.

In this paper, copper octoate has been applied as a homogeneous catalyst for the convenient synthesis of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones) (MbHDMC). Copper octoate exhibited pronounced catalytic activity and was easily separated by simple filtration (Scheme 1).

\[ \text{ArCHO} + 2 \text{Cu(OH)}_2 \rightarrow \text{ArC} = \text{O} + 2 \text{HCl} \]

\[ \text{Cu(OH)}_2 \rightarrow \text{Cu}^{2+} + 2 \text{OH}^- \]

**Scheme 1.** Synthesis of MbHDMC (3) using copper octoate as catalyst.

### Experimental

All the chemicals were purchased from Merck and Sigma-Aldrich companies. Melting points were measured by using the capillary tube method with an Electrothermal 9200 apparatus. \(^1\)H-NMR and \(^{13}\)C-NMR spectra were recorded on a Bruker AQS AVANCE-400 MHz spectrometer, using TMS as an internal standard (CDCl\(_3\) solution). FT-IR spectra were recorded on the FT-IR Bruker Tensor 27. Elemental analyses (% C, H, N) were carried out by Perkin-Elmer 2400 CHN elemental analyzer.

### Synthesis of Copper Octoate

Although this complex is widely available and could be purchased in quite low costs, an example of its preparation has been provided to illustrate the simplicity involved in it which could be counted as another advantage for extending its applications.

To a solution of 2-ethylhexanoic acid (98%, 0.12 mol, 18.00 g) in 100 mL of xylene in a round-bottomed flask, sodium hydroxide (0.12 mol, 5.00 g) solution in 50 mL of water was added. Next, the mixture was stirred and a solution of copper sulfate pentahydrate (0.06 mol, 15.00 g) in 50 mL of water was added drop wise. The mixture was stirred for 1 hour and then the two phases were separated. The organic phase was washed with water and dried by azeotropic distillation in the form of a binary azeotrope of water and xylene, from which the water is removed by distillation using a Dean-Stark apparatus.

### General procedure for the synthesis of MbHDMCs using copper octoate as catalyst

To a solution of aldehyde (1 mmol) and didecane (2 mmol, 0.28 g) in ethanol (5 mL), a solution of copper octoate in xylene (6%, 0.1 mmol, 0.58 g) was added. The solution was refluxed for the amount of time indicated in Table 2. After completion of the reaction as monitored by TLC, using petroleum ether:ethyl acetate (4:1, v:v) as eluent, the reaction mixture was cooled to room temperature and then the precipitated product was simply filtered and washed with ethanol. The catalyst was easily removed to the filtrate in the solvated form in ethanol. For further purification, the products were recrystallized from ethanol. All of the products were known and their physical data were compared with those of authentic samples in the literature and found to be identical.
Physical and spectral data

2,2’-phenylmethylenbis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3a)
Mp: 191 °C; FT-IR (KBr): 3423, 2842, 1593, 1498, 1314, 871 cm⁻¹; ¹H-NMR (δ, 400 MHz, CDCl₃): 1.15 (s, 6H, 2CH₃), 1.27 (s, 6H, 2CH₃), 2.31-2.56 (m, 8H, 4CH₂), 5.54 (s, 1H, CH), 7.08-7.28 (m, 5H, ArH), 9.76 (s, 1H, OH), 11.89 (s, 1H, OH); ¹³C-NMR (δ, 100 MHz, CDCl₃): 26.5, 29.7, 30.1, 32.8, 46.7, 47.4, 116.6, 124.3, 125.5, 128.7, 138.3, 190.4, 190.8; Anal. Calcld. for C₂₃H₂₈O₄: C%, 74.97; H%, 7.66. Found: C%, 74.62; H%, 7.71.

2,2’-(4-methoxyphenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3b)
Mp: 147 °C; FT-IR (KBr): 3596, 1794, 1620, 1403, 1175 cm⁻¹; ¹H-NMR (δ, 400 MHz, CDCl₃): 1.15 (s, 6H, 2CH₃), 1.65 (s, 6H, 2CH₃), 2.34-2.42 (m, 8H, 4CH₂), 3.81 (s, 3H, OCH₃), 5.81 (s, 1H, CH), 6.61 (d, J= 8.1 Hz, 2H, ArH), 6.88 (d, J= 8.1 Hz, 2H, ArH), 12.06 (brs, 2H, OH); ¹³C-NMR (δ, 100 MHz, CDCl₃): 26.8, 29.2, 31.0, 31.9, 45.2, 46.8, 55.9, 113.3, 115.7, 127.5, 129.2, 157.1, 189.1, 190.4; Anal. Calcld. for C₂₆H₂₉O₄: C%, 72.34; H%, 7.59. Found: C%, 72.24; H%, 7.75.

2,2’-(3-nitrophenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3c)
Mp: 194-196 °C; FT-IR (KBr): 3394, 2972, 1599, 1379 cm⁻¹; ¹H-NMR (δ, 400 MHz, CDCl₃): 1.10 (s, 6H, 2CH₃), 1.05 (s, 6H, 2CH₃), 2.36-2.58 (m, 8H, 4CH₂), 5.55 (s, 1H, CH), 7.45-7.50 (m, 2H, ArH), 8.00-8.08 (m, 2H, ArH), 11.85 (brs, 2H, 2OH); ¹³C-NMR (δ, 100 MHz, CDCl₃): 27.22, 29.70, 31.44, 32.85, 46.43, 46.99, 113.12, 121.07, 123.22, 129.16, 133.88, 141.65, 148.46, 189.68, 194.15; Anal. Calcld. for C₂₅H₂₇NO₄: C%, 66.81; H%, 6.58; N%, 3.39. Found: C%, 66.73; H%, 6.80; N%, 3.12.

2,2’-(4-nitrophenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3d)
Mp: 190 °C; FT-IR (KBr): 2962, 1533, 1513, 1375, 1345 cm⁻¹; ¹H-NMR (δ, 400 MHz, CDCl₃): 1.11 (s, 6H, 2CH₃), 1.18 (s, 6H, 2CH₃), 2.47 (m, 8H, 4CH₂), 5.58 (s, 1H, CH), 7.22 (d, J= 8.9 Hz, 2H, ArH), 8.17 (d, J= 8.9 Hz, 2H, ArH), 9.77 (s, 1H, OH), 11.79 (s, 1H, OH); ¹³C-NMR (δ, 100 MHz, CDCl₃): 27.0, 29.6, 32.5, 33.3, 45.4, 47.0, 114.8, 123.1, 127.8, 146.0, 146.4, 189.8, 190.8; Anal. Calcld. for C₂₅H₂₈O₄: C%, 66.61; H%, 6.58; N%, 3.39. Found: C%, 66.65; H%, 6.83; N%, 3.24.

2,2’-(4-methylphenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3e)
Mp: 142 °C; FT-IR (KBr): 3421, 2963, 2640, 1685, 1477, 1383, 1160, 892 cm⁻¹; ¹H-NMR (δ, 400 MHz, CDCl₃): 1.15 (s, 6H, 2CH₃), 1.24 (s, 6H, 2CH₃), 2.32-2.54 (m, 8H, 4CH₂), 5.46 (s, 1H, CH), 2.76 (s, 3H, CH₃), 6.91-7.24 (m, 3H, ArH), 11.58 (s, 1H, OH), 11.92 (s, 1H, OH); Anal. Calcld. for C₂₅H₂₉NO₄: C%, 75.36; H%, 7.91. Found: C%, 75.37; H%, 7.69.

2,2’-(4-N,N-dimethylaminophenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3f)
Mp: 195-197 °C; FT-IR (KBr): 3132, 1605, 1521, 1377, 1315, 1268, 811 cm⁻¹; ¹H-NMR (δ, 400 MHz, CDCl₃): 0.99 (s, 6H, 2CH₃), 1.28 (s, 6H, 2CH₃), 2.30-2.50 (m, 8H, 4CH₂), 3.09 (s, 6H, N(CH₃)₂), 5.46 (s, 1H, CH), 6.69 (d, J= 8.4 Hz, 2H, ArH), 6.98 (d, J= 8.4 Hz, 2H, ArH), 9.53 (s, 1H, OH), 11.95 (s, 1H, OH); Anal. Calcld. for C₂₅H₂₉NO₄: C%, 72.96; H%, 8.08; N%, 3.40. Found: C%, 72.90; H%, 8.23; N%, 3.24.

2,2’-(4-hydroxyphenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3g)
Mp: 190 °C; FT-IR (KBr): 3425, 3083, 1595, 1498, 1374, 1322 cm⁻¹; ¹H-NMR (δ, 400 MHz, CDCl₃): 1.08 (s, 6H, 2CH₃), 1.22 (s, 6H, 2CH₃), 2.45 (m, 8H, 4CH₂), 5.41 (s, 1H, CH), 6.82 (d, J= 8.8 Hz, 2H, ArH).
Results and Discussion

Initially, benzaldehyde was selected as a typical aromatic aldehyde in order to optimize parameters such as the amount of catalyst, solvent, and temperature. The reaction between benzaldehyde (1 mmol) and dimedone (2 mmol) was carried out in ethanol and under reflux. After one hour, the product was obtained in 69% yield. However, in the presence of 15 mol% of copper octoate as catalyst, the yield of the target compound (3a) increased to 90% and the reaction time decreased to 25 min which highlights the effect of the catalyst. To optimize the amount of catalyst, the model reaction was carried out in the presence of different quantities of catalyst. As shown in Table 1, the best result was with 10 mol% of the catalyst. In the next step, we switched to decide the best reaction medium by running the model reaction in other solvents like acetonitrile and chloroform, but no improvement was observed in reaction profiles. Various temperatures were also examined disclosing the fact that the reaction shows a great dependence on temperature and higher temperatures are preferable in terms of reaction times and yields.

With these initial results in hand, we next examined the generality of this method using different aromatic aldehydes with various substitution patterns. These results are collected in Table 2. Under the optimized conditions, irrespective of the substituent present on aromatic ring, the corresponding products were obtained with high yields and purity by simple filtration.

For many years, these target compounds were considered as tetraketones. However, according to spectral data and X-ray diffraction studies [33], a keto-enol form has now been assigned to this class of compounds as the major structure. For example, in 1H-NMR spectra of 3a, three singlet protons have been appeared in 11.89, 9.76, and 5.54 ppm which are attributed to hydroxyl protons and the benzylic proton connected to linker carbon, respectively. The singlet form of these peaks negates the presence of any adjacent proton to the aforementioned protons, which occurs in tetraketone frameworks. In addition, hydroxyl absorption in 3423 cm⁻¹ and carbonyl absorption in 1593 cm⁻¹ in the FT-IR spectra, are other evidences which give more clarification to recommended keto-enol structure.
Table 1. Optimization of the conditions for the model reaction of benzaldehyde with dimedone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amount of catalyst (mol%)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>EtOH</td>
<td>Reflux</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>EtOH</td>
<td>Reflux</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>EtOH</td>
<td>Reflux</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>EtOH</td>
<td>Reflux</td>
<td>25</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>EtOH</td>
<td>Reflux</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>CH₃CN</td>
<td>Reflux</td>
<td>32</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>CHCl₃</td>
<td>Reflux</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>EtOH</td>
<td>25</td>
<td>60</td>
<td>87</td>
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<tr>
<td>9</td>
<td>10</td>
<td>EtOH</td>
<td>40</td>
<td>45</td>
<td>88</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>EtOH</td>
<td>60</td>
<td>30</td>
<td>91</td>
</tr>
</tbody>
</table>

Table 2. Synthesis of various MbHDMCs catalyzed by copper octoatea.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Found mp (°C)</th>
<th>Reported mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>3a</td>
<td>24</td>
<td>91</td>
<td>191</td>
<td>190-191 [35]</td>
</tr>
<tr>
<td>2</td>
<td>4-OMeC₆H₄</td>
<td>3b</td>
<td>35</td>
<td>88</td>
<td>147</td>
<td>146-148 [25]</td>
</tr>
<tr>
<td>3</td>
<td>3-NO₂C₆H₄</td>
<td>3c</td>
<td>16</td>
<td>89</td>
<td>194-196</td>
<td>190-191 [27]</td>
</tr>
<tr>
<td>4</td>
<td>4-NO₂C₆H₄</td>
<td>3d</td>
<td>20</td>
<td>90</td>
<td>190</td>
<td>189 [35]</td>
</tr>
<tr>
<td>5</td>
<td>4-MeC₆H₄</td>
<td>3e</td>
<td>50</td>
<td>91</td>
<td>142</td>
<td>139-141 [25]</td>
</tr>
<tr>
<td>6</td>
<td>4-N(Me)₂C₆H₄</td>
<td>3f</td>
<td>27</td>
<td>88</td>
<td>195-197</td>
<td>195-196 [34]</td>
</tr>
<tr>
<td>7</td>
<td>4-OC₆H₄</td>
<td>3g</td>
<td>45</td>
<td>89</td>
<td>190</td>
<td>189 [35]</td>
</tr>
<tr>
<td>8</td>
<td>4-BrC₆H₄</td>
<td>3h</td>
<td>40</td>
<td>88</td>
<td>173-176</td>
<td>172-174 [28]</td>
</tr>
</tbody>
</table>

*aReaction Conditions: aldehyde (1 mmol), dimedone (2 mmol), 6% xylene solution of copper octoate (0.1 mmol, 0.58 g), EtOH (5 mL), reflux.

On the other hand, according to the symmetrical appearance of the structures of the products, it is initially expected that ³H-NMR spectrum of these compounds would be clear and uncrowded ones exhibiting two hydroxyl protons in the same chemical shift; while in fact, the number of signals are more than what was anticipated and hydroxyl groups appeared at δ 11.89 and 9.76 ppm. These distinguished chemical shifts disclose the asymmetric character of the structure of the product which could be simply explained by the intramolecular hydrogen bonds, decreasing the asymmetry of the molecule effectively (Figure 2). Indeed, the formation of intramolecular hydrogen bonds restricts the rotation around the methylene bridge and locks the molecule in a rigid asymmetric form in which one of the hydroxyl groups is settled close to the benzylic proton and probably corresponds to the high-field signal while the other hydroxyl proton next to the Ar group is related to the low-field signal. In other words, the methylene bridge acts as a chiral center inducing a diastereotopic relationship between the hydroxyl groups. Kaupp et al. demonstrated the presence of intramolecular hydrogen bonds as two almost identical O-H...O hydrogen bridges by B3LYP/6-31G calculations. The formation of these hydrogen bridges was attributed to molecular tendency for minimizing its energy levels [35]. Similar interpretations were also made by several groups to illustrate the presence of intramolecular hydrogen bonds in bis(coumarin) derivatives [36-38] (Figure 2).
Figure 2. Intramolecular hydrogen bonding in MbHDMC and biscoumarin derivatives.

A possible mechanism for this reaction is demonstrated in Figure 3. Lewis acid-catalyzed Knoevenagel condensation of aldehyde (1) and dimedone (2) results in the formation of the intermediate (4), which on addition of the second molecule of dimedone, the target MbHDMC (3) is formed. The blockage of the reaction at this stage, the reluctance for dehydration of (3), and formation of the corresponding xanthene could be attributed to the mild essence of copper octoate and also the fact that the desired product (3) gradually precipitates from the reaction solution and practically interrupts the function of homogeneous copper octoate catalyst.

Figure 3. Plausible mechanism for the copper octoate-catalyzed synthesis of MbHDMCs.

After completion of each reaction, the reaction mixture was cooled to room temperature and the precipitated product was simply filtered and washed with ethanol. For evaluating the reusability of the catalyst, the filtrate was heated to remove the excess of ethanol and reduce the volume to approximately 5.6 mL (the amount of ethanol required as solvent for the next run plus the xylene solution of the copper octoate). To the concentrated solution remained, the starting materials of the model reaction were simply added and the resulted solution was heated to reflux. As it is exhibited in Table 3, the recycled catalyst solution promoted reactions in a similar manner without significant loss of activity.

In order to prove the merit of copper octoate functioning as a homogeneous catalyst in the synthesis of MbHDMCs, the results obtained for the model reaction in the present work has been compared with previously reported methods in Table 4.

As it is obviously illustrated, the yield obtained using copper octoate as catalyst is almost comparable to other catalysts and conditions but reaction time has been shortened remarkably to amount which is rarely achieved by other approaches presented.

Table 3. Evaluating the reusability of the catalyst.

<table>
<thead>
<tr>
<th>Run</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>85</td>
</tr>
</tbody>
</table>
Table 4. Comparison of the efficiency of copper octoate with other reagents and conditions for the synthesis of (3a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Condition/Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Urea</td>
<td>US, 50 °C/H₂O</td>
<td>1</td>
<td>94</td>
<td>[27]</td>
</tr>
<tr>
<td>2</td>
<td>ZnO</td>
<td>reflux, CH₃CN</td>
<td>12</td>
<td>92</td>
<td>[39]</td>
</tr>
<tr>
<td>3</td>
<td>HClO₄·SiO₂</td>
<td>reflux, H₂O</td>
<td>0.5</td>
<td>91</td>
<td>[40]</td>
</tr>
<tr>
<td>4</td>
<td>EDDA*</td>
<td>reflux, THF</td>
<td>4</td>
<td>88</td>
<td>[30]</td>
</tr>
<tr>
<td>5</td>
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<td>Ball-milling</td>
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* Ethylenediamine diacetate.

** This work.

## Conclusion

In summary, copper octoate as an extensively used industrial reagent has been introduced as a mild Lewis acid catalyst for the synthesis of MbHDMCs. Fine tuning of reaction conditions such as the strength of the catalyst and even solvent plays a critical role in controlling progress of the reaction in the desired level since harsh reaction conditions may result in cyclodehydration and formation of the byproduct of xanthene. In this reaction, the dramatic effect of copper octoate being acidic enough to accelerate the reaction up to very short times in one hand and mild enough to terminate reaction after formation of Michael adducts on the other hand, is quite noticeable. This behavior could be useful in lots of other synthetic processes. In fact, non-corrosive and green character, low cost, and commercial availability are features making it a superior choice as catalyst in organic transformations specially those having an emphasize on the homogeneity of the catalyst.
Acknowledgments

The authors are thankful to Alzahra Research Council for partial financial support.

References


Synthesis and Comparative Antibacterial Studies of some Benzylidene Monosaccharide Benzoates

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Abstract: Methyl α-D-glucopyranoside on reaction with benzaldehyde followed by direct dimolar benzoylation afforded 4,6-O-benzylidene-protected 2,3-di-O-benzoate 3 in good yield. Regioselective monobenzoylation of methyl α-D-mannopyranoside employing dibutyltin oxide method furnished 3-O-benzoate 5. Compound 5, on treatment with excess benzaldehyde followed by direct benzoylation, provided 2,3-di-O-benzoate 7 in high yield. In vitro antibacterial activity studies of the synthesized compounds along with the precursor materials (1-7) were evaluated against ten bacterial pathogens. The structure activity relationship study revealed that the benzoylmannopyranosides (5-7) exhibited more antibacterial inhibitory property as compared to that of glucopyranosides (2-3).


Keywords: Monosaccharide, benzoylation, antibacterial activity, structure activity relationship (SAR).

Introduction

Monosaccharides are wide spread in nature, being a component of some plant glycosides and bacterial polysaccharides of immunological importance [1-2]. Monosaccharide derivatives, especially acylated monosaccharides (esters), have synthetic utility as versatile intermediates in the syntheses of many natural products and their analogues which have great medicinal importance [3-4]. Various methods for acylation of monosaccharides have so far been developed and employed successfully such as direct acylation [5-6], protection-deprotection technique [7], organotin (dibutyltin oxide or dibutyltin oxide) mediated regioselective acylation [8-10] etc. Yet, regioselective acylation (esterification) is a prominent challenge as monosaccharides contain several hydroxyl groups of similar reactivity. In this context, enzyme catalyzed acylation [11] and microwave assisted acylation [12] were also investigated in the past decade. In the present synthetic strategy, we employed direct acylation technique for both methyl α-D-glucopyranoside (1) and methyl α-D-mannopyranoside (4). We have also used dibutyltin oxide method for the regioselective 3-O-benzylation of mannopyranoside 4.

The emergence of multiple antibiotic resistant pathogenic bacteria represents a growing threat to human health worldwide. Thus, search for new antibacterial agents with novel mode of action represents a major target in chemotherapy [13]. Acylated sugars (esters) have been widely used as cosmetic and pharmaceutical industries for many years because they are considered biocompatible, biodegradable, and nontoxic [14-15].
In $^1$H NMR analysis of 1 in DMSO-$d_6$, aromatic protons appear at 8.58, 8.28, 8.02, 7.59, 7.11, 7.05 ppm as a doublet, singlet, multiple, triplet, doublet and doublet, respectively. The OH proton appear at 10.28 ppm as singlet. The $^1$H NMR spectra of the compounds 2 and 3 are somewhat broader than corresponding signals in the compound 1 due to aggregation of the phthalocyanine isomers which is frequently encountered at the concentrations used for NMR spectroscopy. The inner NH protons of 2 were also identified in the $^1$H NMR spectra with a broad chemical shift at -4.03 ppm. In $^{13}$C NMR analysis of 1 in DMSO-$d_6$, aromatic carbons appear at 158.53, 146.53, 135.11, 130.37, 129.48, 129.01, 128.38, 128.33, 127.87, 126.51, 126.11, 123.50, 123.16, 120.22, and 116.35 ppm, C-OH group appeared at 153.49 ppm, nitrile carbons appeared at 115.72 and 114.87 ppm, respectively.

In the EI+ mass spectrum of 1, the presence of the characteristic molecular ion peak at m/z 298.0 [M]+ confirmed the proposed structure. In the case of 2, the molecular ion peak was found at m/z 1233.5 [M+K]+ according to MALDI-TOF spectrum (Fig. 1). Also, the molecular ion peak for compound 3 found at m/z = 1260.7 [M+2]+. The elemental analyses were satisfactory.

**Materials and Methods**

**Chemicals and Apparatus**

FT-IR spectra were recorded on an FT-IR spectrometer (Shimadzu, IR Prestige-21) using CHCl3 mulls. Thin layer chromatography (TLC) was performed on Kieselgel GF254 and visualization was accomplished by spraying the plates with 1% H2SO4 followed by heating the plates at 150-200 °C until coloration took place. $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra were recorded using CDCl3 as a solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and J values are given in Hz. Melting points (mp) were determined on an Electrothermal melting point apparatus and are uncorrected. Evaporations were performed under diminished pressure on a Büchi rotary evaporator. All reagents used were commercially available (Aldrich) and were used as received unless otherwise specified.

**Synthesis**

**Methyl 4,6-O-benzylidene-a-D-glucopyranoside (2):** Benzaldehyde (3.0 g, 28.27 mmol) was added to methyl a-D-glucopyranoside (1) (0.4 g, 2.06 mmol) followed by addition of anhydrous zinc chloride (1.0 g, 7.337 mmol) at room temperature. The reaction mixture was stirred for 12 h and filtered through Celite® 545. Ice was added to the filtrate with constant shaking and the mixture was extracted several times with n-hexane to remove unreacted benzaldehyde. The aqueous layer was then extracted with ethyl acetate (3x5 mL) with occasional warming. The organic layer was dried (MgSO4), and concentrated under reduced pressure to yield a residue which, upon chromatographic purification with n-hexane/ethyl acetate (1/2, v:v), yielded the title compound 2 (0.401 g, 69%) as a white crystalline solid, mp 162-163 °C (lit. [22], mp 163-164 °C).

Rf = 0.48 (n-hexane/ethyl acetate = 1/2, v:v). FT-IR (CHCl3, ν, cm⁻¹): 3310-3400 (OH). $^1$H NMR (400 MHz, CDCl3, δ, ppm): 7.53-7.47 (2H, m, Ar-H), 7.42-7.35 (3H, m, Ar-H), 5.54 (1H, s, PhCH-), 4.80 (1H, d, J= 4.0 Hz, H-1), 4.30 (1H, dd, J= 9.7 and 4.4 Hz, H-6a), 3.94 (1H, dd, J= 9.3 and 9.2 Hz, H-3), 3.82 (1H, ddd, J= 10.3, 9.2 and 4.4 Hz, H-5), 3.75 (1H, dd, J= 10.3 and 9.7 Hz, H-6b), 3.64 (1H, dd, J= 9.2 and 4.0 Hz, H-2), 3.50 (1H, dd, J= 9.3 and 9.2 Hz, H-4), 3.47 (3H, s, OCH3). $^{13}$C NMR (100 MHz, CDCl3): δ 137.1 (Ar-C), 129.3, 128.3, 126.3 (Ar-CH), 102.0 (PhCH-), 99.7 (C-1), 80.8 (C-4), 72.9 (C-2), 71.9 (C-3), 68.9 (C-6), 62.4 (C-5), 55.6 (OCH3).
Methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-a-D-glucopyranoside (3): A solution of compound 2 (0.3 g, 1.281 mmol) in dry pyridine (1 mL) was cooled to 0 °C whereupon benzoyl chloride (0.396 g, 2.817 mmol) and DMAP (cat.) were added to it. The mixture was stirred overnight at room temperature. Usual work-up and silica gel column chromatography furnished the di-O-benzoyl derivative, 3 (0.521 g, 92%) as a crystalline solid. Recrystallization from ethyl acetate-n-hexane gave the analytically pure sample as colorless needles, mp 146-148 °C.

\[ R_f = 0.51 \text{ (n-hexane/ethyl acetate = 4/1, v/v).} \]

FT-IR (CHCl₃, ν, cm⁻¹): 1735, 1719 (CO).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3, \delta, ppm): 7.81-8.05 \text{ (5H, m, Ar-H), 7.31-7.48 (6H, m, Ar-H), 7.21-7.30 (4H, m, Ar-H), 6.02 (1H, t, } J = 9.8 \text{ Hz, H-3), 5.52 (1H, s, PhCH=), 5.21 (1H, dd, } J = 9.8 \text{ and 3.6 Hz, H-2), 5.13 (1H, d, } J = 3.6 \text{ Hz, H-1), 4.28-4.32 (1H, m, H-5), 4.03 (1H, t, } J = 9.7 \text{ Hz, H-4), 3.78-3.87 (2H, m, H-6a and H-6b), 3.37 (3H, s, OCH}_3. \]

Methyl 3-O-benzoyl-a-D-mannopyranoside (5): To a solution of methyl a-D-mannopyranoside (4) (0.3 g, 1.545 mmol) in dry methanol (10 mL) was added dibutyltin oxide (Bu₂SnO) (0.423 g, 1.699 mmol) and the mixture was heated under reflux. After 2 h the reaction mixture became homogeneous and clear. The mixture was then refluxed for an additional hour and the solvent was evaporated off in vacuo to leave a white solid. The solid tin complex was suspended in dry 1,4-dioxane (3 mL) and benzoyl chloride (0.239 g, 1.70 mmol) was slowly added to this solution, with stirring, at room temperature. The solution became clear upon addition of benzoyl chloride and stirring

was continued for 4 h. The solvent was evaporated off in vacuo to leave a syrupy mass, which was subjected to column chromatography (chloroform/methanol = 6/1, v/v) to give 3-O-benzoate 5 (0.313 g, 68%) as a thick syrup [1].

\[ R_f = 0.48 \text{ (chloroform/methanol = 4/1, v/v).} \]

FT-IR (CHCl₃, ν, cm⁻¹): 3260-3350 (br OH), 1746 (CO). \[ ^1H \text{ NMR (400 MHz, CDCl}_3, \delta, ppm): 7.55-7.73 \text{ (5H, m, Ar-H), 6.07 (1H, dd, } J = 10.0 \text{ and 3.1 Hz, H-3), 4.62 (1H, d, } J = 1.5 \text{ Hz, H-1), 4.22 (1H, dd, } J = 3.1 \text{ and 1.5 Hz, H-2), 4.13 (1H, dd, } J = 12.1 \text{ and 5.2 Hz, H-6a), 3.91-3.97 \text{ (1H, m, H-5), 3.88 (1H, app t, } J = 9.8 \text{ Hz, H-4), 3.75 (1H, dd, } J = 12.1 \text{ and 2.0 Hz, H-6b), 3.16 (3H, s, OCH}_3. \]

Methyl 3-O-benzoyl-4,6-O-benzylidene-a-D-mannopyranoside (6): A solution of the 2,4,6-triol 5 (0.4 g, 1.341 mmol) in dry benzaldehyde (3.0 g, 28.27 mmol) was treated with anhydrous zinc chloride (1.0 g, 7.337 mmol) at room temperature. The reaction mixture was stirred at this temperature overnight and filtered through celite. Usual work-up as described for compound 2 and chromatographic purification (n-hexane/ethyl acetate = 1/2, v/v) yielded the title compound 6 (0.389 g, 75%) as white needles, mp 135-136 °C.

\[ R_f = 0.45 \text{ (n-hexane/ethyl acetate = 3/1, v/v).} \]

FT-IR (CHCl₃, ν, cm⁻¹): 3290-3500 (br OH), 1735 (CO). \[ ^1H \text{ NMR (400 MHz, CDCl}_3, \delta, ppm): 8.05(2H, d, } J = 8.1 \text{ Hz, Ar-H), 8.05 (1H, t, } J = 7.6 \text{ Hz, Ar-H), 7.39-7.46 (5H, m, Ar-H), 7.27-7.35 (2H, m, Ar-H), 5.59 (1H, s, PhCH=), 5.54 (1H, dd, } J = 10.4 \text{ and 3.2 Hz, H-3), 4.78 (1H, d, } J = 1.2 \text{ Hz, H-1), 4.32 (1H, dd, } J = 3.2 \text{ and 1.2 Hz, H-2), 4.22-4.31 (2H, m, H-5 and H-6a), 3.95-4.03 (1H, m, H-6b), 3.92 (1H, t, } J = 10.1 \text{ Hz, H-4), 3.43 (3H, s, OCH}_3. \]

Methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-a-D-mannopyranoside (7): The reaction of compound 6 (0.3 g, 0.776 mmol) and benzoyl chloride (0.396 g, 2.817 mmol) in anhydrous pyridine (1 mL) at 0 °C to room temperature for overnight followed by chromatography (n-hexane/ethyl acetate =10/1, v/v) gave the di-O-benzoyl derivative, 7 (0.343 g, 90%) as a white crystalline solid. Recrystallization from ethyl acetate/n-hexane (1/1, v/v) gave the analytically pure sample as needles, mp 121-122 °C.
\( R_i = 0.51 \) (n-hexane/ethyl acetate = 4/1, v/v). FT-IR (CHCl\textsubscript{3}, \( \nu \), cm\textsuperscript{-1}): 1687, 1682 (CO). 
\( \textsuperscript{1}H \) NMR (400 MHz, CDCl\textsubscript{3}, \( \delta \), ppm): 8.12-8.19 (5H, m, Ar-H), 7.57-7.69 (4H, m, Ar-H), 7.41-7.54 (6H, m, Ar-H), 5.81 (1H, dd, \( J = 10.0 \) Hz, H-3), 5.79 (1H, dd, \( J = 3.1 \) and 1.2 Hz, H-2), 5.69 (1H, s, PhCH\textsubscript{2}), 4.93 (1H, d, \( J = 1.2 \) Hz, H-1), 4.32-4.41 (2H, m, H-5 and H-6a), 4.11-4.19 (1H, m, H-6b), 4.00 (1H, t, \( J = 10.0 \) Hz, H-4), 3.50 (3H, s, OCH\textsubscript{3}).

**Antibacterial screening tests**

Four Gram-positive bacteria viz. *Bacillus cereus* BTCC 19, *Bacillus megaterium* BTCC 18, *Bacillus subtilis* BTCC 17 and *Staphylococcus aureus* ATCC 6538 and six Gram-negative bacteria viz. *Escherichia coli* ATCC 25922, INABAET (vibrio) AE 14748, *Pseudomonas aeruginosa* CRL (ICDDRB), *Salmonella paratyphi* AE 14613, *Salmonella typhi* AE 14612, and *Shigella dysenteriae* AE 14369 were selected for antibacterial potentiality test. For the detection of antibacterial activities, the disc diffusion method described by Bauer et al. [23] was followed. Mueller-Hinton (agar and broth) medium was used for the culture of bacteria. Dimethylformamide (DMF) was initially used as a solvent to prepare the desired solution (1%) of the compounds. The plates were incubated at 37 °C for 48 h. Proper control was maintained with DMF. Each experiment was carried out in triplicate. All the results were compared with the standard antibacterial antibiotic ampicillin [50 μg/disc, Beximco Pharmaceuticals Ltd., Bangladesh].

**Results and Discussion**

Our main aim was to synthesize 2,3-di-O-benzoyl derivatives (3 and 7) of methyl α-D-glucopyranoside (1) and methyl α-D-mannopyranoside (4), respectively, to study and compare their antibacterial properties.

**Synthesis of methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-α-D-glucopyranoside (3)**

Initially we prepared methyl 4,6-O-benzylidene-α-D-glucopyranoside (2) from methyl α-D-glucopyranoside (1). The reaction of methyl α-D-glucopyranoside (1) with benzaldehyde in the presence of anhydrous zinc chloride for 12 h followed by work-up and chromatography gave a white crystalline solid, mp 162-163 °C (Scheme 1). The FT-IR spectrum of this solid showed bands at 3310-3400 cm\textsuperscript{-1} corresponding to hydroxyl stretching. In its \( \textsuperscript{1}H \) NMR spectrum, a two-proton multiplet at δ 7.53-7.47, a three-proton multiplet at δ 7.42-7.35 and a one-proton singlet at δ 5.54 clearly indicated the formation of benzylidene acetal in the molecule. This was also confirmed by its \( \textsuperscript{13}C \) NMR spectrum where signals at δ 137.1 (Ar-C), 129.3, 128.3, 126.3 (Ar-CH) and 102.0 (PhCH\textsubscript{2}) were found for the benzylidene acetal. Complete analysis of its FT-IR, \( \textsuperscript{1}H \) and \( \textsuperscript{13}C \) NMR spectra led us to assign the structure as methyl 4,6-O-benzylidene-α-D-glucopyranoside (2).

![Scheme 1](image-url)

**Scheme 1.** Reagents and conditions: (a) PhCHO, dry ZnCl\textsubscript{2}, 25 °C, 12 h, 69%. (b) BzCl, dry pyridine, 0 °C-RT, 12 h, 92%.
Having protected glucopyranoside 2 in hand, we carried out its dibenzoylation (Scheme 1). Thus, treatment of glucopyranoside 2 with dimolar benzoyl chloride (BzCl) in anhydrous pyridine for 12 h using a catalytic amount of DMAP gave a compound almost in quantitative yield (92%) as needles, mp 146-148 °C. In the FT-IR spectrum of this compound, bands at 1735 and 1719 cm⁻¹ were observed for carbonyl frequency and hence indicated the attachment of benzoyloxy groups in the molecule. The FT-IR spectrum showed no band for hydroxyl stretching. In the ¹H NMR spectrum, the following peaks were observed in the aromatic region: δ 7.81-8.05 (5H, m), 7.31-7.48 (6H, m) and 7.21-7.30 (4H, m) and a one-proton singlet at δ 5.52 for PhCH-. The more ten aromatic protons in addition to benzylidene acetal protons indicated the attachment of two benzoyloxy groups in the molecule. Also, H-2 (at δ 5.21 as dd) and H-3 (at δ 6.02 as t) protons shifted down field as compared to its precursor compound 2. This confirmed the attachment of benzoyloxy groups at position C-2 and C-3. So, the structure was established as methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-a-D-glucopyranoside (3).

**Synthesis of methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-a-D-mannopyranoside, 7**

Our next attempt was to synthesize methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-a-D-mannopyranoside, (7). For this reason we prepared methyl 3-O-benzoyl-a-D-

![Scheme 2](image)

**Scheme 2.** Reagents and conditions: (a) Bu₂SnO, dry MeOH, reflux, 3h, BzCl, dioxane, RT, 4h, 68%. (b) PhCHO, dry ZnCl₂, 25 °C, 12 h, 65%. (c) BzCl, 0 °C-RT, 12 h, 90%.

In the dibutyltin oxide method initially a stannylene ring (intermediate tin complex) is formed between cis-vicinal glycol at C-2 and C-3 position, where the equatorial C-3 OH group is activated without exception (Figure 1). Hence the unimolecular benzoylation occurs at C-3 position only. Thus, the structure of this compound was established as methyl 3-O-benzoyl-a-D-mannopyranoside (5) by analyzing its FT-IR and ¹H NMR spectra.

![Intermediate tin complex](image)

**Figure 1.** Formation of the intermediate stannylene ring.
The 3-O-benzoate 5 was then subjected for 4,6-O-benzylidene protection. Thus, the reaction of compound 5 with benzaldehyde in the presence of anhydrous zinc chloride for 12 h followed by work-up and chromatography gave as white needles, mp 135-136 °C. The FT-IR spectrum of this solid showed bands at 3290-3500 (br) and 1735 cm\(^{-1}\) corresponding to hydroxyl and carbonyl stretchings, respectively. In its \(^1\)H NMR spectrum, a two-proton doublet at \(\delta\) 8.05, a one-proton triplet at \(\delta\) 8.05, a five-proton multiplet at \(\delta\) 7.39-7.46, a two-proton multiplet at \(\delta\) 7.27-7.35 and a one-proton singlet at \(\delta\) 5.59 (PhCH-) clearly indicated the formation of benzylidene acetal and presence of a benzoyl group in the molecule. Complete analysis of its FT-IR and \(^1\)H NMR spectra led us to assign the structure as methyl 3-O-benzoyl-4,6-O-benzylidene-\(\alpha\)-D-mannopyranoside (6).

Having protected mannopyranoside 6 in hand, we carried out its 2-O-benzylation. Thus, unimolar benzylation of 6 with benzoyl chloride in pyridine and chromatography gave a crystalline solid. Recrystallization from ethyl acetate/\(n\)-hexane (1:1, v:v) gave the analytically pure sample as needles, mp 121-122 °C (Scheme 2). The FT-IR spectrum showed no band for hydroxyl stretching. In the FT-IR spectrum of this compound, bands at 1687 and 1682 cm\(^{-1}\) were observed for carbonyl frequency. In the \(^1\)H NMR spectrum of this compound the following peaks were observed in the aromatic region: \(\delta\) 8.12-8.19 (5H, m), 7.57-7.69 (4H, m), 7.41-7.54 (6H, m) and a one-proton singlet at \(\delta\) 5.69 (PhCH-).

The additional five aromatic protons than that of 3-O-benzoate 6 indicated the attachment of one more benzoxyloxy groups in the molecule. Also, H-2 (at \(\delta\) 5.79 as dd) protons shifted down field as compared to its precursor compound 6. Thus, the structure of the compound was assigned as methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-\(\alpha\)-D-mannopyranoside (7).

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**Antibacterial activities of the synthesized compounds**

The results of the in vitro inhibition zone against the selected Gram-positive bacteria due to the effect of the chemicals (1-7) are mentioned in Table 1. It was observed from Table 1 that the tested chemicals were less effective against these Gram-positive organisms. Only methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-\(\alpha\)-D-mannopyranoside (7) exhibited considerable inhibition (*20 mm) against Bacillus cereus which was comparable to that of the standard antibiotic, ampicillin (*22 mm).

### Table 1. Inhibition against Gram-positive organisms by the tested chemicals (1-7).

<table>
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<th>Compound no.</th>
<th>Diameter of zone of inhibition, in mm (50 µg, dw / disc)</th>
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<tr>
<td>7</td>
<td>*20</td>
</tr>
<tr>
<td><strong>Ampicillin</strong></td>
<td>*22</td>
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</table>

NB. "N/A" indicates no inhibition, dw = dry weight, "***" indicates standard antibiotic, "**" shows good inhibition.
Inhibition zone against the selected Gram-negative bacteria due to the effect of the monosaccharides (1-7) are mentioned in Table 2. The test chemicals showed better activity against these organisms as compared to that of Gram-positive organisms. The compounds (1-7) did not show considerable inhibition against *E. coli* and INABAET (vibrio). The study revealed that the tested chemicals were more effective against *Salmonella paratyphi* and *Salmonella typhi*.

<table>
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<tr>
<th>Compound no.</th>
<th>E. coli</th>
<th>INABAET (vibrio)</th>
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<th><em>Salmonella paratyphi</em></th>
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<th>Shigella dysenteriae</th>
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NB. N/A indicates no zone of inhibition. dw= dry weight. ** indicates standard antibiotic, * shows good inhibition.

**Structure activity relationship (SAR)**

In *vitro* antibacterial study revealed that the monosaccharide derivatives (1-7) were more active against some Gram-negative organisms than that of Gram-positive organisms. An important observation was that the benzoylated mannosylpyranoside (5-7) were more active than that of the glucopyranosides (2-3). Again, compounds 1, 2 and 4 showed poor toxicity than that of compounds 3, 6, and 7 against these pathogens. This is probably due to the presence of more hydroxyl groups in 1, 2 and 4. While compounds 3, 6 and 7 having fewer or no hydroxyl groups showed much better antibacterial potentiality (mannopyranoside 5 was found to be exceptional). Here the hydrophobicity of the molecules increased gradually from compounds 1, 2, and 4 to 3, 6, and 7. The hydrophobicity of compounds is an important parameter for bioactivity and is directly related to membrane permeation [25]. We believe that similar hydrophobic interaction might occur between the benzoyl groups of monosaccharides (3 and 7) accumulated in the lipid membranes of bacteria. As a consequence of their hydrophobic interaction, bacteria lose their membrane permeability [26], ultimately causing death of the bacteria.
Conclusion

We have synthesized methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-a-D-glucopyranoside (3) and methyl 4,6-O-benzylidene-2,3-di-O-benzoyl-a-D-mannopyranoside (7) from methyl a-D-glucopyranoside (1) and methyl a-D-mannopyranoside (4), respectively in reasonably good yields. A comparative in vitro antibacterial study of these compounds was carried out successfully employing ten bacterial pathogens. The structure activity relationship (SAR) study revealed that the benzoylated mannopranosides (5-7) were more active against the tested organisms than that of the glucopyranosides (1-3).

Acknowledgments

We are grateful to the Research Cell, University of Chittagong for research grant (Sl. no. 83/07, 2014) to carry out the research work. We would like to thank Dr. M.S. Rahman, Department of Microbiology, University of Chittagong, for the antibacterial tests of the synthesized compounds.

References


Synthesis and antioxidant activity of some novel derivatives of bis-2-azetidinones and bis-4-thiazolidinones

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Abstract: In present study, several bis-2-azetidinones 2a-g and bis-4-thiazolidinones 3a-g have been synthesized from ethylenediaminebis-Schiff bases using conventional as well as microwave techniques. The newly synthesized compounds were established on the basis of spectroscopic techniques. Further, all compounds were screened for antioxidant activity; most of the titled compounds show potent activity.


Keywords: Bis-Schiff bases, bis-2-azetidinones, bis-4-thiazolidinones, microwave technique, antioxidant activity.

Introduction

Literature survey reveals that most of the compounds having thiazolidinones and azetidinones nuclei possess pharmacological activity [1, 2]. Azetidinones which are part of antibiotic structures are known to exhibit interesting biological activities. A large number of 3-chloro monocyclic β-lactams possesses powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant and antitubercular activities [3-5]. They also function as enzyme inhibitors and are effective on the central nervous system [6-8]. 4-Thiazolidinones and its derivatives are known to possess a variety of physiological viz. analgesic local [9] and spiral [10] antimicrobial [11], hypnotics [12], antibacterial [13], antifungal [14], antitubercular [15], anticancer and anti-HIV [16]. The classical synthesis of these compounds involves cycloaddition of monochloroacetyl chloride with imine (Schiff base) resulting in the formation of 2-azetidinone (β-lactam) [17]. Conventional synthesis of 4-thiazolidinones involves the cyclocondensation between the Schiff base and mercaptoacetic acid [18, 19]. As part of our interest towards the development of novel heterocycles [20-24], herein we wish to report the synthesis of bis-2-azetidinones 2a-g and bis-4-thiazolidinones 3a-g by the reaction of bis-imines 1a-g with chloroacetyl chloride and thioglycolic acid, respectively, using conventional as well as microwave technique (Scheme 1).
Materials and Methods

Chemicals and Apparatus

Melting points were determined in an open capillary tube and are uncorrected. FT-IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. 1H NMR spectra were recorded on a Gemini 300-MHz instrument in DMSO as solvent and TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. Synthos-3000, Anton Paar reaction system was used for microwave synthesis.

Synthesis of bis-Schiff bases (1a-g)

Compounds 1a-g were synthesized according to given method in literature [31]. 1,2-ethylenediamine (0.001 mole) and aldehyde (0.002 mole) were dissolved in ethanol (15 mL), acetic acid (0.2 mL) was added, and the reaction mixture was refluxed for 2-15 min. Reaction was monitored on TLC. Half of the solvent was evaporated and the rest was cooled. The separated solid was filtered, washed with water, and crystallized from ethanol.

General procedure for preparation of bis-2-azetidinones (2a-g); conventional technique

Synthesis of 1,1-ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxy-5-iodophenyl)azetidin-2-one (2c)

A solution of bis (3-ethoxy-4-hydroxy-5-iodophenyl)benzylidene-1,2-ethylenediamine (0.001 mole, 0.463 mg) in dry dioxane (15 mL) was added to well stirred mixture of chloroacetyl chloride (0.004 mole) and triethyl amine (0.006 mole) in dry 1,4-dioxane at 0°C. The reaction mixture was stirred for 6 hrs. Excess of solvent was distilled and the resultant solid was poured into ice-cold water. The separated solid was filtered and recrystallized from alcohol to give 2c.

Microwave technique

Synthesis of 1,1-ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxy-5-iodophenyl)azetidin-2-one (2c)

A mixture of bis(3-ethoxy-4-hydroxy-5-iodophenyl)benzylidene-1,2-ethylenediamine (0.001 mole, 0.463 mg) in dry dioxane (15 mL) was taken in conical flask, and chloroacetyl chloride (0.004 mole) and triethyl amine (0.006 mole) were added slowly at 0-5 °C. Then the reaction mixture was transferred to microwave reaction vessel equipped with a magnetic stirrer (Synthos-3000). The vessel was sealed and the reaction mixture was irradiated by 50 W intermittently at 30 sec. interval for 5 min. The solid so formed was recrystallized from ethyl alcohol to give 2c. Some of the physical data of the synthesized compounds 2a-g are given in Table 1.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxyphenyl)azetidin-2-one (2a)

FT-IR (KBr cm⁻¹): 3480 (Ar-OH stretching), 1670 (C=O stretching), 1470, 1450 (Aromatic C=C stretching), 1380 (C-N stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 1.35 (t, 6H, -2CH₃), 2.80 (s, 2H, -2CH), 3.68 (s, 4H, -2NCH₂), 4.15 (q, 4H, -2OCH₂), 5.06 (s,2H,-2CH-CI), 6.32-7.51 (m, 6H, -2ArH). MS (m/z): 509(M+). Anal. calcd. for C₂₄H₂₈Cl₂N₂O₆: C,56.58; H, 5.10. Found: C, 55.28; H, 5.35.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxy-5-bromophenyl)azetidin-2-one) (2b)

FT-IR (KBr cm⁻¹): 3435 (Ar-OH stretching), 1685 (C=O stretching), 1455, 1440 (Aromatic C=C stretching), 1380, 1385 (C-N stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 1.38 (t, 6H, -2CH₃), 2.85 (s, 2H, -2CH), 3.70 (s, 4H, -2NCH₂), 4.01 (q, 4H, -2OCH₂), 5.12 (s,2H,-2CH-CI), 6.53-7.80 (m, 4H, -2ArH), 13.01(s,2H,-2Ar-OH). MS (m/z): 667 (M+). Anal. calcd. for C₂₄H₂₄Br₂Cl₂N₂O₆: C,43.76; H, 3.90. Found: C,43.28; H, 3.35.
1,1-Ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxy-5-iodophenyl)azetidin-2-one) (2c)

FT-IR (KBr cm⁻¹): 3410 (Ar-OH stretching), 1690 (C=O stretching), 1440, 1425 (Aromatic C=C stretching), 1370 (C-N stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 1.35 (t, 6H, -2CH₃), 2.83 (s, 2H, -2CH), 3.65 (s, 4H, -2NCH₂), 4.15 (q, 4H, -2OCH₂), 5.16 (s, 2H, -2CH=Cl), 6.65-7.85 (m, 4H, -2ArH), 13.10 (s, 2H, -2Ar-Oh). MS (m/z): 761 (M+). Anal. calcd. for C₂₅H₂₄Cl₂I₂N₂O₂: C, 37.56; H, 3.15. Found: C, 37.28; H, 3.35.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-methoxy-4-hydroxyphenyl)azetidin-2-one) (2d)

FT-IR (KBr cm⁻¹): 3425 (Ar-OH stretching), 1678 (C=O stretching), 1460, 1444 (Aromatic C=C stretching), 1378 (C-N stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.82 (s, 2H, -2CH), 3.40 (s, 4H, -2NCH₂), 3.75 (s, 6H, -2OCH₃), 5.01 (s, 2H, -2CH=Cl), 6.25-7.30 (m, 6H, -2ArH), 13.60 (s, 2H, -2Ar-Oh). MS (m/z): 483 (M+). Anal. calcd. for C₂₅H₂₄Cl₂N₂O₆: C, 54.56; H, 4.96. Found: C, 54.80; H, 4.30.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-methoxy-4-hydroxy-5-bromophenyl)azetidin-2-one) (2e)

FT-IR (KBr cm⁻¹): 3445 (Ar-OH stretching), 1682 (C=O stretching), 1465, 1450 (Aromatic C=C stretching), 1380 (C-N stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.83 (s, 2H, -2CH), 3.43 (s, 4H, -2NCH₂), 3.78 (s, 6H, -2OCH₃), 5.12 (s, 2H, -2CH=Cl), 6.30-7.35 (m, 4H, -2ArH), 13.40 (s, 2H, -2Ar-Oh). MS (m/z): 613 (M+). Anal. calcd. for C₂₅H₂₂Br₂Cl₂N₂O₆: C, 43.06; H, 3.58. Found: C, 43.80; H, 3.30.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-methoxy-4-hydroxy-5-chlorophenyl)azetidin-2-one) (2f)

FT-IR (KBr cm⁻¹): 3480(Ar-OH stretching), 1668 (C=O stretching), 1475, 1455 (Aromatic C=C stretching), 1385 (C-N stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.86 (s, 2H, -2CH), 3.47 (s, 4H, -2NCH₂), 3.80 (s, 6H, -2OCH₃), 5.20 (s, 2H, -2CH=Cl), 6.42-7.40 (m, 4H, -2ArH), 13.32 (s, 2H, -2Ar-Oh). MS (m/z): 556 (M+). Anal. calcd. for C₂₅H₂₂Cl₂I₂N₂O₆: C, 47.48; H, 3.95. Found: C, 47.76; H, 4.00.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-methoxy-4-hydroxy-5-iodophenyl)azetidin-2-one) (2g)

FT-IR (KBr cm⁻¹): 3428 (Ar-OH stretching), 1681 (C=O stretching), 1460, 1445 (Aromatic C=C stretching), 1382 (C-N stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.85 (s, 2H, -2CH), 3.42 (s, 4H, -2NCH₂), 3.69 (s, 6H, -2OCH₃), 5.15 (s, 2H, -2CH=Cl), 6.35-7.25 (m, 4H, -2ArH), 13.10 (s, 2H, -2Ar-Oh). MS (m/z): 640 (M+). Anal. calcd. for C₂₅H₂₂Cl₂I₂N₂O₆: C, 41.25; H, 3.43. Found: C, 41.80; H, 3.56.

General procedure for preparation of bis-4-thiazolidinone

Conventional synthesis of 3,3-ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxy-5-iodophenyl)-1,3-thiazolidin-4-one) (3c)

A mixture of bis(3-ethoxy-4-hydroxy-5-iodophenyl)benzylidene-1,2-ethylenediamine (0.001 mole, 0.462 mg) in 1,4-dioxane (15 mL) containing anhydrous ZnCl₂ (0.02 g) and thioglycolic acid (0.002 mole) was refluxed for 8 hrs. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered and recrystallized from 1,4-dioxane to give 3c.

Microwave technique

Synthesis of 3,3-ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxy-5-iodophenyl)-1,3-thiazolidin-4-one). (3c)

A homogeneous mixture of bis(3-ethoxy-4-hydroxy-5-iodophenyl)benzylidene-1,2-ethylenediamine (0.001 mole, 0.462 mg) in 1,4-dioxane (15 mL) containing anhydrous ZnCl₂ (0.02 g) and thioglycolic acid (0.002 mole) was introduced to a microwave reaction vessel equipped with a magnetic stirrer (Synthos-3000). The vessel was sealed and the reaction was irradiated by 50 W intermittently at 30 sec. interval for 5 min. The solid formed was filtered and recrystallized from ethyl alcohol to give 3c. Some of the physical data of synthesized compounds 3a-g are given in Table 2.
3,3-Ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxyphenyl)-1,3-thiazolidin-4-one(3a))

FT-IR (KBr cm⁻¹): 3525 (Ar-OH stretching), 1792 (C=O stretching), 1570, 1530,1440 (Aromatic C=C stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 1.30 (t, 6H, -2CH₃), 3.29 (s, 2H, -2CH), 4.19 (q, 4H, -2OCH₃), 5.10 (s,4H,-2CH₂-S), 7.20-7.95 (m, 6H, -2ArH), 13.01 (s, 2H, -2Ar-OH). MS (m/z): 504 (M⁺). Anal. calcd. for C₁₂₅H₁₂₅N₂O₅S₂: C,57.24; H, 5.50. Found: C,57.80; H, 5.56.

3,3-Ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxy-5-bromophenyl)-1,3-thiazolidin-4-one(3b))

FT-IR (KBr cm⁻¹): 3535 (Ar-OH stretching), 1795 (C=O stretching), 1575, 1540,1450 (Aromatic C=C stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 1.36 (t, 6H, -2CH₃), 3.32 (s, 2H, -2CH), 4.21 (q, 4H, -2OCH₃), 5.16 (s,4H,-2CH₂-S), 7.30-7.85 (m, 4H, -2ArH), 13.0 (s,2H,-2Ar-OH). MS (m/z): 662 (M⁺). Anal. calcd. for C₁₂₇H₁₂₇Br₂N₂O₅S₂: C,43.50; H, 3.92. Found: C,43.70; H, 3.96.

3,3-Ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxy-5-iodophenyl)-1,3-thiazolidin-4-one(3c))

FT-IR (KBr cm⁻¹): 3530(Ar-OH stretching), 1790 (C=O stretching), 1555, 1530,1450 (Aromatic C=C stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 1.28 (t, 6H, -2CH₃), 3.29 (s, 2H, -2CH), 4.18 (q, 4H, -2OCH₃), 4.96 (s,4H,-2CH₂-S), 7.35-7.75 (m, 4H, -2ArH). MS (m/z): 756 (M⁺). Anal. calcd. for C₁₂₇H₁₂₇I₂N₂O₅S₂: C, 38.09; H, 3.43. Found: C,38.26; H, 3.56.

3,3-Ethane-1,2-diylbis(2-(3-methoxy-4-hydroxyphenyl)-1,3-thiazolidin-4-one(3d))

FT-IR (KBr cm⁻¹): 3525 (Ar-OH stretching), 1788 (C=O stretching), 1553, 1540,1435 (Aromatic C=C stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 3.30 (s, 2H, -2CH), 3.50 (s, 4H, -2NCH₃), 3.70 (s, 6H, -2OCH₃), 4.86 (s,4H,-2CH₂-S), 7.38-7.80 (m, 6H, -2ArH), 12.05 (s,2H,-2Ar-OH). MS (m/z): 476 (M⁺). Anal. calcd. for C₁₆₇H₁₆₇N₂O₆S₂: C,55.46; H, 5.04. Found: C,54.50; H, 5.25.

3,3-Ethane-1,2-diylbis(2-(3-methoxy-4-hydroxy-5-bromophenyl)-1,3-thiazolidin-4-one(3e))

FT-IR (KBr cm⁻¹): 3540 (Ar-OH stretching), 1793 (C=O stretching), 1558, 1545,1440 (Aromatic C=C stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 3.32 (s, 2H, -2CH), 3.53 (s, 4H, -2NCH₃), 3.73 (s, 6H, -2OCH₃), 4.88 (s,4H,-2CH₂-S), 7.40-7.85 (m, 4H, -2ArH), 12.14 (s, 2H, -2Ar-OH). MS (m/z): 634 (M⁺). Anal. calcd. for C₁₂₇H₁₂₇Br₂N₂O₅S₂: C, 41.64; H, 3.47. Found: C,41.30; H, 3.80.

3,3-Ethane-1,2-diylbis(2-(3-methoxy-4-hydroxy-5-chlorophenyl)-1,3-thiazolidin-4-one(3f))

FT-IR (KBr cm⁻¹): 3550 (Ar-OH stretching), 1794 (C=O stretching), 1568, 1555, 1450 (Aromatic C=C stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 3.35 (s, 2H, -2CH), 3.56 (s, 4H, -2NCH₃), 3.78 (s, 6H, -2OCH₃), 4.89 (s,4H,-2CH₂-S), 7.43-7.85 (m, 4H, -2ArH), 13.14 (s, 2H, -2Ar-OH). MS (m/z): 546 (M⁺). Anal. calcd. for C₁₂₇H₁₂₇Cl₂N₂O₅S₂: C, 48.35; H, 4.09. Found: C, 48.20; H, 4.20.

3,3-Ethane-1,2-diylbis(2-(3-methoxy-4-hydroxy-5-iodophenyl)-1,3-thiazolidin-4-one(3g))

FT-IR (KBr cm⁻¹): 3520 (Ar-OH stretching), 1790 (C=O stretching), 1550, 1530,1452 (Aromatic C=C stretching). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 3.27 (s, 2H, -2CH), 3.41 (s, 4H, -2NCH₃), 3.69 (s, 6H, -2OCH₃), 4.81 (s,4H,-2CH₂-S), 7.31-7.75 (m, 4H, -2ArH), 13.01 (s, 2H, -2Ar-OH). MS (m/z): 728 (M⁺). Anal. calcd. for C₁₆₇H₁₆₇I₂N₂O₆S₂: C,36.26; H, 3.02. Found: C, 36.40; H, 4.30.
Antioxidative activity
The following antioxidative methods were used to evaluate the antioxidative properties of our test compounds.

**DPPH• Scavenging Activity**
DPPH is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, the methanolic solution of DPPH shows a strong absorption band at 517 nm. DPPH radical reacts with various electron donating molecules (reducing agents or antioxidants). When electrons become paired off, the result is that DPPH solution is bleached. This results in the formation of the colorless 2,2'-diphenyl-1-picryl hydrazine. Reduction of the DPPH radicals can be estimated quantitatively by measuring the decrease in absorbance at 517 nm.

Procedure: Equal volumes of 100 µM 2,2'-diphenyl-1-picrylhydrazyl (DPPH) in methanol was added to different concentrations of test compounds (0 – 200 µM/mL) in methanol, mixed well and kept in dark for 20 min. The absorbance at 517 nm was measured using the Shimadzu UV-1650 spectrophotometer. Plotting the percentage DPPH• scavenging against concentration gave the standard curve and the percentage scavenging was calculated from the following equation:

\[
\% \text{scavenging} = \frac{\text{Absorbance of blank} - \text{Absorbance of test}}{\text{Absorbance of blank}} \times 100
\]

IC50 was obtained from a plot between concentration of test compounds and % scavenging. Ascorbic acid was used as standard for comparison.

![Structural changes occur with DPPH during oxidation](image)

**Nitric Oxide Scavenging Activity**
Nitric oxide (NO) will be generated by sodium nitroprusside in solution. In the presence of an antioxidant or nitric oxide scavenger, the amount of NO generated will be less. The excess NO will be estimated by Griess reagent, which is the mixture of sulfanilic acid and naphthylethylenediamine dihydrochloride. The nitric oxide will give pink colored complex estimated at 540 nm.

Procedure: To a reaction mixture (6 mL) containing sodium nitroprusside (10 mM, 4 mL), phosphate buffer saline (PBS, 1.0 mL) and 1.0 mL of different concentration of test compounds/standard were incubated at 25°C for 150 min. After incubation, 0.5 mL of the reaction mixture containing nitrate was removed and 1.0 mL of sulfanilic acid was added, mixed well and allowed to stand for 5 min for completion of diazotization. Then 1.0 mL of naphthylethylenediamine dihydrochloride was added, mixed and allowed to stand for 30 min in dark at room temperature.
The absorbance of these solutions was measured at 540 nm against corresponding blank solution without sodium nitroprusside [29-30]. The % scavenging and IC50 values were determined as explained in DPPH assay.

## Results and discussion

In view of the importance of this class of heterocycles and in continuation of our earlier investigations, we have reported the synthesis of 4-thiazolidinones from imines and some of the thiazolidinones were found to have antibacterial action [25]. Therefore, in the present paper, we synthesized a new class of bis-2-azetidinones and bis-4-thiazolidinones by cyclocondensation reaction of imines 1a-g (Scheme 1). The halo-substituted hydroxybenzaldehydes required for the preparation of imines were prepared by iodination of substituted hydroxybenzaldehydes using molecular iodine and iodic acid by refluxing technique [26]. The 1a-g on cyclocondensation with chloroacetyl chloride afford bis-2-azetidinones 2a-g and with thioglycolic acid afford bis-4-thiazolidinones 3a-g using both conventional as well as MWI techniques. MWI technique were used over conventional technique due to the application of microwave (MW) irradiation as a non-conventional energy source for activation of reactions has now become a very popular and useful technology in organic chemistry [27]. Many researchers have described accelerated organic reactions towards proving the synthetic utility of MW irradiation in routine organic synthesis [28]. Thus, MW techniques has many advantages including easy work-up procedure, short reaction time, and does not need any effort for isolation of products giving high percentage yields. The structures of newly synthesized compounds 2a-g & 3a-g respectively, have been confirmed by elemental analysis, FT-IR, NMR and MS spectral studies. In 1H NMR spectra of bis-2-azetidinones obtained at δ value 2.85 and δ near 5.0 is due to proton of CH-N and CH-Cl respectively. The 1H NMR spectra of bis-4-thiazolidinones show characteristics δ value at 4.90 due to two protons of –CH2S. The δ value at 3.32 is due to –CH of five-membered thiazolidinone ring.

![Scheme 1](attachment:image.png)

**Scheme 1:** Synthesis of some novel derivatives of bis-2-azetidinones and bis-4-thiazolidinones
The DPPH is a stable radical that can accept hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, alcoholic solution of DPPH shows a strong absorption at 517 nm. Therefore, DPPH readily reacts with reducing agent to yield colorless 2, 2'-diphenyl -1-picrylhydrazine. Reduction of the DPPH radicals can be determined quantitatively by measuring the decrease in absorbance at 517 nm.

Nitric oxide is generated by sodium nitroprusside in solution. In the presence of an antioxidant, the amount of NO generated will be less. The excess of NO estimated by Griess reagent, which is composed of the mixture of H₂SO₄ and naphthylethylene diamine.

The results of antioxidant activity expressed as IC50 value with two different antioxidant agents are shown in Table 3. The compounds 2c, 2f, 3c and 3f were tested using DPPH scavenging method and they showed IC50 value at 70.20, 70.28, 70.30, and 70.13 μM, when compared with that of the standard ascorbic acid at 69.08 μM, respectively. However the compound 2d and 2e did not show significant activity. Further, the antioxidant studies carried out using NO scavenging method, the only compounds 2c, 2g, 3c, and 3g showed IC50 value at 92.10, 91.25, 92.00 and 92.20 μM in comparison with standard, respectively. The compounds 2e and 3e did not show antioxidant activity.

### Table 1: Physical and analytical data for bis-2-azetidinones.

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<th>Entry</th>
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<th>% yield, MW</th>
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<td>H</td>
<td>158</td>
<td>68</td>
<td>80</td>
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<tr>
<td>2b</td>
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<td>Br</td>
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<td>2c</td>
<td>OEt</td>
<td>I</td>
<td>220</td>
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<tr>
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<td>OMe</td>
<td>H</td>
<td>150</td>
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<tr>
<td>2e</td>
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<td>OMe</td>
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<tr>
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<td>OMe</td>
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### Table 2: Physical and analytical data for bis-4–thiazolidinones.

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<th>% yield, MW</th>
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<td>85</td>
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<td>I</td>
<td>160</td>
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<tr>
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<td>70</td>
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<tr>
<td>3g</td>
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Table 3: Antioxidant activity of bis-2-azetidinones and bis-4-thiazolidinones.

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<th>Entry</th>
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<th>NO scavenging (µM)</th>
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## Conclusion

In conclusion, the salient feature of our approach is coupling microwave with keeping modernization over classical procedure for the synthesis of bis-2-azetidinones and bis-4-thiazolidinones. The microwave technique is found to be efficient and cheap for the synthesis of mentioned compounds. In continuation of previously published results [32] and as a part of our research work, focus has been given on the development of new bis-2-azetidinones and bis-4-thiazolidinones as a bioactive agents. Synthesis and preliminary antioxidant screening of new bis-2-azetidinones and bis-4-thiazolidinones have been demonstrated. The presence of halogen atom in the compounds provides a positive influence on antioxidant activity. Owing to encouraging results, it was found that the synthesized compounds have broader value of activity than standard used for screening of antioxidant activity. The electronic effect also played a role in activity, as can be screen for the compounds having electron donor character such as −OEt, −OMe and −OH. Thus in future, this class of compounds may be used as templates for generating better lead molecules as a antioxidant agents.

## Acknowledgment

The authors gratefully acknowledge to Principal, N.E.S. Science College, Nanded, for providing laboratory facilities and Director Indian Institute of Chemical Technology (IICT), Hyderabad for providing necessary instrumental facilities.
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Synthesis and characterization of near-IR absorbing metal-free and zinc(II) phthalocyanines modified with aromatic azo groups

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Abstract: Metal-free and zinc(II) phthalocyanine complexes bearing peripheral (E)-4-((2-hydroxynaphthalen-1-yl)diazenyl) units have been synthesized. Novel phthalonitrile derivative required for the preparation of phthalocyanine complexes was prepared by coupling 4-aminophthalonitrile and 2-naphthol. The structures of these new compounds were characterized by using elemental analyses, proton and carbon nuclear magnetic resonance, fourier transform infrared spectroscopy, ultraviolet–visible spectrophotometry, fluorescence spectrophotometry, and mass spectrometry. In the UV-Vis spectra a broad absorption band appears for phthalocyanine complexes at around 450–500 nm resulting from the azo-group introduced onto the phthalocyanine ring. The photophysical properties of metal-free and zinc(II) phthalocyanines were studied in tetrahydrofuran.


Keywords: Phthalocyanines; synthesis; 2-naphthol; azobenzene; fluorescence.

Introduction

Organic colorants are being extensively studied because of numerous advantageous properties with many areas of possible applications. Phthalocyanines (Pcs) are important classes of these organics which have a highly conjugated pi-electron system. Interest of the Pcs still arises due to their excellent chemical and physical properties which give potential application in many fields of science and technology such as non-linear optics, gas sensors, electrocatalysis, solar cells, and sensitizers for photodynamic cancer therapy [1-6]. Pcs have high photosensitivity in the near-infrared region (650–850 nm). However, they exhibit a low optical absorption in the visible region (450–650 nm), and cannot be used in white light imaging processes. These properties of Pcs may be modulated by introducing substituent groups on peripheral, non-peripheral or axial positions, changing the symmetry of the Pc molecule, or introducing different metal cations into the cavity of the Pc ring [7-10].

Another class of organic colorants is azo compounds, are used in various areas, such as textiles, electro-optical devices, lasers, and ink-jet printers. They consist of one or more conjugated chromophore azo (−N=N−) groups in their structures. Due to their conjugated structures, azo compounds show intense absorptions in the visible region (450–650 nm) [11-13].

Although many kinds of Pcs and azo compounds have been widely used in many fields, azo group substituted Pcs are still scarce [14-17]. When Pcs and azo groups are included in the same framework, the components bring along their useful properties to the whole molecule. We therefore initiated a study on the mixed arrays of Pcs and azo compounds. In this study, we have reported synthesis and characterization of azo group modified Pcs containing naphthyl groups on the periphery.
Materials and Methods

All chemicals and reagents were purchased from major suppliers and used without any further purification. All reported \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on an Agilent VNMRS 500 MHz spectrometer. Chemical shifts (\(\delta\), ppm) were determined with TMS as the internal reference. FT-IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR (ATR sampling accessory) spectrometer, electronic spectra were recorded on a Scinco LabProPlus UV-Vis spectrophotometer. Fluorescence spectra were recorded on a Perkin-Elmer LS55 fluorescence spectrophotometer. Mass spectra were measured on a Bruker microflex LT MALDI-TOF MS spectrometer and Perkin Elmer Clarus 500 mass spectrometer in positive electron impact mode. The isotopic patterns for all assigned signals are in agreement with the calculated natural abundance. Data have been given for the most abundant isotope only. Melting points were determined on a Büchi Melting Point B-540 apparatus. Elemental analyses were performed on a Thermo Flash EA 1112. The homogeneity of the products was tested in each step by TLC (SiO\(_2\)). 4-Aminophthalonitrile was prepared according to the reported procedure [16].

Synthesis

**Synthesis of (E)-4-((2-hydroxynaphthalen-1-yl)diazenyl)phthalonitrile (1)**

4-Aminophthalonitrile (0.715 g, 5.0 mmol) was stirred and dissolved in a mixture of 10 mL of deionized water and 16 mL of concentrated hydrochloric acid until a clear solution was obtained. This solution was cooled to 0–5 °C, and then a solution of NaNO\(_2\) (0.552 g, 8.0 mmol) in 10 mL of deionized water was added dropwise to the first solution. On the other hand, 2-naphthol (0.720 g, 5.0 mmol) was dissolved in 5 mL of 10% NaOH, cooled to 0–5 °C and then added to the solution of 3,4-dicyanobenzenediazonium chloride in small portions. Solid product immediately precipitated. The resulting mixture was stirred for further an hour at room temperature. The precipitate was filtered off, washed several times with water. The product was purified by crystallization with from ethanol. Yield: 0.641 g (43%); mp > 200 °C; anal. calcd. for C\(_{18}\)H\(_{10}\)N\(_2\)O: C, 72.48; H, 3.38; N, 18.76%. Found: 72.59; H, 3.39; N, 18.76%. IR: \(\nu_{max}\) cm\(^{-1}\) 3182 (OH), 3056 (Ar-CH), 2226 (C=≡N), 1597 (C=C), 1479 (C=N). \(^1\)H NMR (DMSO-d\(_6\)): \(\delta\), ppm 10.28 (s, H, -OH) 8.58 (d, H, Ar-H), 8.28 (s, H, Ar-H), 8.02 (m, 4H, Ar-H), 7.59 (t, H, Ar-H), 7.11 (d, H, Ar-H), 7.05 (d, H, Ar-H). \(^{13}\)C NMR (DMSO-d\(_6\)): \(\delta\), ppm 158.53 (aromatic C), 153.49 (aromatic C-OH), 146.53 (aromatic C-H), 135.11 (aromatic C=H), 130.37 (aromatic C=H), 129.48 (aromatic C), 129.01 (aromatic C-H), 128.38 (aromatic CH), 128.33 (aromatic C=H), 127.87 (aromatic C), 126.51 (aromatic C-H), 126.11 (aromatic C), 123.50 (aromatic C), 123.16 (aromatic C-H), 120.22 (aromatic C), 116.35 (aromatic C), 115.72 (C≡N), 114.87 (C≡N). UV-Vis (THF): \(\lambda_{max}\) nm (log \(\varepsilon\)) 310 (4.43), 447 (4.62). MS (EI\(^+\)): m/z 298.0 [M\(^+\)].

**Metal-free phthaloxyanine (2)**

Metallic lithium (0.134 g, 19.291 mmol) was suspended in 2 mL of n-pentanol and heated at 90 °C with stirring until a homogeneous mixture containing lithium pentanolate was formed. Then phthalonitrile derivative 1 (0.200 g, 0.671 mmol) was added to the reaction mixture and temperature was raised to 140 °C. The mixture was stirred for additional two hours. After cooling to room temperature the green crude product was precipitated with water and then 2 mL of concentrated hydrochloric acid was added to this mixture. In this mixture, the Li\(_2\)Pc was converted into H\(_2\)Pc. The precipitate was filtered off and washed with methanol, ethanol, hexane, chloroform, and acetone then dried in vacuo.
Results and Discussion

Synthesis and Characterization

In this study, the synthesis of (E)-4-((2-hydroxynaphthalen-1-yl)diazeyln)phthalonitrile (1) obtained by diazotization of 4-aminophthalonitrile and coupling with 2-naphthol in 10% NaOH solution. Diazonium cation was produced by treating the 4-aminophthalonitrile with nitrous acid (NaNO₂/HCl) at 0–5 °C for two hours. All spectroscopic data of newly synthesized phthalonitrile derivative (1) show a good agreement with proposed structures.

Cyclotetramerization of the phthalonitrile derivative (1) to the metal-free phthalocyanine (2) was accomplished by “Li method” in pentanol at reflux temperature in a sealed tube. The direct conversion of Li₂Pc to the metal-free complex 2 was achieved by addition of concentrated HCl to the solution of Li₂Pc. Compound 1 reacted with anhydrous Zn(CH₃COO)₂ in the presence of a catalytic amount of DBU via a template-oriented reaction in pentanol at refluxed temperature to obtain the zinc(II) phthalocyanine derivative (3) (Scheme 1). In this study, synthesized tetra-substituted phthalocyanine compounds (2 and 3) were obtained as mixture of four region-isomers of D₂ᵥ, Cᵥ, Cᵥ and Cᵥ, symmetries for similar physical and chemical properties. Both of synthesized phthalocyanines were soluble in DMF and DMSO, but insoluble in common organic solvents such as methanol, ethanol, hexane, chloroform, and acetone. The purification of complexes 2 and 3 was carried out by washing with methanol, ethanol, hexane, chloroform, and acetone. FT-IR, ¹H NMR, UV-Vis, elemental analysis, and mass characterization techniques were used to shed light into the structure of the novel PCs (2 and 3). Spectral data of the novel compounds were in very good agreement with expected structures.

In the FT-IR spectrum of phthalonitrile derivative 1, aromatic CH, aromatic C=C, azo group (N=N) stretching vibrations appeared at 3056, 1597, and 1479 cm⁻¹, respectively. The presence of the OH group was confirmed by the observation of broad OH stretching at 3182 cm⁻¹. In addition, the characteristic vibration of the C≡N appears at 2226 cm⁻¹, after conversion of the dinitrile into the phthalocyanine, the sharp peak for the C≡N vibration completely disappeared. The FT-IR spectra of the phthalocyanines 2 and 3 are very similar, except NH stretching band at 3257 cm⁻¹ in the inner core of metal-free phthalocyanine 3.
Scheme 1. Synthetic route for phthalonitrile (1) and phthalocyanines (2 and 3) (i: HCl, Fe, CH₃OH; ii: HCl, NaNO₂, 0 °C; iii: 2-naphthol, 10% NaOH, 0–5 °C; iv: a) Metallic lithium, n-pentanol, reflux; b) Zn(CH₃COO)₂, DBU, n-pentanol, reflux).

In the ¹H NMR analysis of 1 in DMSO-d₆, aromatic protons appear at 8.58, 8.28, 8.02, 7.59, 7.11, 7.05 ppm as a doublet, singlet, multiplet, triplet, doublet and doublet, respectively. The OH proton appeared at 10.28 ppm as singlet. The ¹H NMR spectra of the compounds 2 and 3 are somewhat broader than corresponding signals in the compound 1 due to aggregation of the phthalocyanine isomers which is frequently encountered at the concentrations used for NMR spectroscopy. The inner NH protons of 2 were also identified in the ¹H NMR spectra with a broad chemical shift at -4.03 ppm.

In ¹³C NMR analysis of 1 in DMSO-d₆, aromatic carbons appear at 158.53, 146.53, 135.11, 130.37, 129.48, 129.01, 128.38, 128.33, 127.87, 126.51, 126.11, 123.50, 123.16, 120.22, and 116.35 ppm, C-OH group appeared at 153.49 ppm, nitrile carbons appeared at 115.72 and 114.87 ppm, respectively.
In the EI+ mass spectrum of 1, the presence of the characteristic molecular ion peak at m/z 298.0 [M]+ confirmed the proposed structure. In the case of 2, the molecular ion peak was found at m/z 1233.5 [M+K]+ according to MALDI-TOF spectrum (Fig. 1). Also, the molecular ion peak for compound 3 found at m/z = 1260.7 [M+2]+. The elemental analyses were satisfactory.

![Figure 1. MALDI-TOF MS spectrum of compound 2.](image)

**Ground state electronic absorption spectra**

The simplest Pc unit is a 18-n electron system giving rise to electronic spectra with two strong absorption regions, one of them is in the UV region at about 300–400 nm (B band) and the other one is in the visible region at about 600–700 nm (Q band), both correlating to n-n* transitions. The absorption spectra of 2 and 3 in THF were shown in Figs. 3 and 4. The Soret bands are observed at 330 nm for complex 2 and 345 nm for complex 3. The Q band, of complex 2, is somewhat different from complex 3, with a split Q band indicating lower symmetry (D_{2h}) of the metal-free derivative. The Q-band regions of the UV-Vis spectra are red-shifted into the near-IR region at 658 and 727 nm for complex 2 and at 734 nm for complex 3. Due to the great extension of n-conjugation by four peripheral azo-dye moieties, the Q-bands of 2 and 3 are significantly red-shifted as compared to tetra-tert-butylyphthalocyanines [4]. In addition, the extension of n-conjugation as well as aggregation in solution also leads to peak broadening. The precursor 1 and phthalocyanine complexes (2 and 3) produce intense absorptions from 450 to 550 nm (Figs. 2–4). This kind of additional absorptions is really uncommon, and might suggest some novel opto-electronic properties to the Pcs.
**Figure 2.** UV spectrum of 1 in THF.

**Figure 3.** UV spectrum of 2 in THF.

**Figure 4.** UV spectrum of 3 in THF.
Fluorescence spectra

The steady-state fluorescence spectra of phthalocyanine derivatives (2 and 3) were performed in THF, upon excitation at the 650 nm Q-band vibration for 2 and excitation at the 670 nm Q-band vibration for 3. Emission around 744 nm for 2 and 755 nm for 3 (Fig. 5), occurred almost entirely from the phthalocyanine moiety. The Q bands of phthalocyanine derivatives’ (2 and 3) luminescent spectra are red-shifted when compared to the corresponding peripherally substituted phthalocyanine complexes. The red-shifts observed in emission maxima are 40-60 nm bathochromically shifted in comparison with peripherally substituted phthalocyanine complexes [19]. Essentially, the energy gap (ΔE) between the S₀ and S₁ becomes smaller, resulting a bathochromic shift [19].

The excitation spectra of 2 and 3 were similar to absorption spectra and both were mirror images of the fluorescent spectra in THF. The proximity of the wavelength of the Q-band absorption to the Q-band maxima of the excitation spectra for ZnPc suggest that the nuclear configurations of the ground and excited states are similar and are not affected by excitation in THF [20-22]. Excitation spectra of H₂Pc (2) show two shoulders in the red spectral region because of the lowering of symmetry [23].

Comparative method [Eq. (1)] was used to determine the quantum yields of the compounds (2 and 3) as described in [24, 25]. In this method, the quantum yield of a compound is determined by using a standard which has similar fluorescence properties as the tested compound has. All measurements of the standard and the compound must be performed at the same environmental conditions with the same instrumental settings.

\[
\Phi_f = \Phi_f(Std) \frac{FA_{Std} \eta^2}{F_{Std} A_{Std} \eta_{Std}^2}
\]

(1)

Where F and F_{Std} are the areas under the fluorescence curves of phthalocyanines derivatives and the standard, respectively. A and A_{Std} are the respective absorbance of the sample and standard at the excitation and η and η_{Std} are the refractive indices of solvents used for the sample and standard, respectively. ZnPc was employed as a standard in DMF (Φ_f = 0.23) [26]. The fluorescence quantum yield (Φ_f) values for the complexes were found to 0.14 for H₂Pc (2) and 0.19 for ZnPc (3). The Φ_f values of all the studied Pc complexes are lower than unsubstituted ZnPc.

It implies that the presence of the substituents (azo group) certainly results in fluorescence quenching, due to enhancement of intersystem crossing (ISC) by the presence of a heavier azo-naphthol groups in these complexes [27]. The Stokes' shifts ranged from 15 to 20 nm, typical of Pc complexes [28-29].

Conclusion

In this study, modified phthalocyanines having azo group and bearing naphthol units on the periphery were successfully prepared. The new compounds were characterized by using elemental analyses, ¹H NMR, UV-Vis and FT-IR spectroscopy and mass spectrometry. The results confirmed their proposed structures. The complexes (2 and 3) have good solubility in THF, DMF and DMSO. The Q bands of the phthalocyanine complexes (2 and 3) were red-shifted compared to the peripherally substituted metal-free and zinc phthalocyanine complexes. These complexes (2 and 3) produce an intense absorption from 450 to 500 nm and might suggest for some novel opto-electronic devices.
The fluorescence behaviors of the phthalocyanine complexes (2 and 3) were studied in THF. Generally, the $\Phi_F$ values of these complexes are lower than unsubstituted ZnPc.

**Figure 5.** Excitation and emission spectra of 2 and 3 in THF. Excitation wavelengths: 650 nm for 2 and 670 nm for 3.

**Acknowledgments**

This work was supported by the Research Fund of the Istanbul Technical University.

**References**


Theoretical Investigations for the Behavior of Hydrotropes in Aqueous Solution

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Abstract: The presented paper introduces an attempt for finding a theoretical model capable for describing the critical aggregation concentration (cac) for some hydrotropes (a series of sodium-p-n-alkylbenzoates, n=0-8). Such a proposal was carried out through theoretical calculations based on density functional theory (DFT) for estimating some physical properties which might be helpful for supporting the recent published report as all of these hydrotropes are considered as surfactant like (see doi: 10.1021/la2025846). The estimated physical properties can be divided to three classes according to their effect: steric properties such as volume and surface area, electronic properties such as polarizability, and hydrophobic properties such as log P which represents the ratio of concentrations of a compound in two phases of octanol and water. The results show that both steric and hydrophobic properties play major roles in predicting the cac for the presented hydrotropes. The best model was found between cac and tail polarizability (PT) according to the following relation: cac = 1.52-1.09log PT ; with $r^2$ equal to 0.96, S.E equal to 0.026 M and significant cross validation correlation coefficient (0.943). A unique feature of the presented model is containing only one descriptor with excellent statistical parameters. This actually supports the recent (above mentioned) published results of that all of these hydrotropes can be considered as surfactant-like. The suggested models were applied to some randomly selected surfactants with reasonable results. The results are generally suggesting for the possibility of estimating the cac or critical micelle concentration (cmc) for amphiphilic molecules using computational chemistry software.


Keywords: Density functional theory (DFT), Qualitative structure property relationship (QSPR), Hydrotropes, Critical aggregation concentration (cac), Critical micelle concentration (cmc), Surfactant, Sodium-p-n-alkylbenzoates.

Introduction

In recent years, hydrotropes as amphiphilic organic molecules has long been a special topic due to their special characteristics, giving the possibility for their employment in many aspects [1, 2]. However, a clear and general definition of hydrotropes still need verification [3,4]. For instance, hydrotropes are divided into two classes from self-assembly point of view; surfactant-like and unlike. In other words, the chain length of hydrophobic part of hydrotrope plays the major role on the last classification. Recently, Hopkins Hatzopoulos et al.[5] investigated the physicochemical properties of a homologous series of sodium p-n-alkylbenzoates (Scheme 1). They stated according to their results of small angle neutron scattering (SANS) technique and surface tension analysis that all of these hydrotropes display as surfactant like behaviors with no regard to the chain length. Subsequently, they have supported this event through studying the effects of structure variation on physicochemical behavior of hydrotropes composed of sodium phenyl-n-alkanoates and cyclohexyl-n-alkanoates [6].
Actually, such a surprising phenomenon was attracted us for theoretical verification using quantum mechanical calculations. According to the literature, there is no theoretical study based on quantum mechanical methods that have been performed for hydrotrpores. Such kind of a study was only found for surfactant molecules. For instance, Huibers studied the electrical charge distribution in some ionic surfactants using quantum chemical calculations [7]. He indicated that the partial charge distribution influences surfactant self-assembly and physical properties. Other publications based on employing the quantitative structure-property relationship (QSPR) have been found for a considerable number of anionic surfactants [7-14]. A part of complexity for the prediction of descriptors has been mostly shown by these investigations. For examples, the Kier and Hall descriptor was calculated indirectly through many parameters [13].

![Chemical structure of sodium p-n-alkylbenzoates](image)

**Scheme 1.** Chemical structure of sodium p-n-alkylbenzoates; n=0-8.

Thus, the presented paper introduces theoretical investigations using density functional theory (DFT) and qualitative structure property relationship (QSPR) calculations that might be helpful for understanding the recent published results of hydrotrpores [5]. It should be noted that we have recently used these hydrotrpores to develop a theoretical model that used for evaluating the critical packing parameter of self-assembled amphiphilic molecules [15]. The obtained results were indirectly supporting that the members of all studied hydrotrpores family may be considered as surfactant-like.

## Theoretical section

The experimental cac values of used hydrotrpores (sodium p-n-alkylbenzoates, n=0-8) were taken from Reference 5. The experimental cmc of all selected surfactants were taken from Reference 16. The chemical structural inputs for all presented molecules and their models were prepared by using HyperChem 8.0.8 program package. Each of the structures was employed as a starting point for energy minimization using molecular mechanics MM2, semi-empirical PM3 and DFT methods according to our developed procedure that has already listed in the related published research [15]. In this method, a series of computational operations have been suggested in order to reach the best method from accuracy and time-consuming points of views. In other words, our treatments deal with relatively huge molecules (surfactants) which need long periods of time if one uses large or medium basis set for computation process. Therefore, considerable efforts have been paid in order to find an accurate method using small basis set. It has been found that the use of molecular mechanics for a conformational analysis and then a geometric optimization with DFT at relatively small basis set (3-21G) and B3LYP hybrid functional is a significant tool to search for the global minima [15].
This procedure eliminates the significance of using large and medium basis sets which therefore the time consumed for this process is comparatively very short. The selected properties of the presented molecules were estimated from their optimized structures. Finally, Minitab program (MINITAB Release 14.1, www.minitab.com) was used for regression analysis of the calculated data.

Results and discussion

The recent observation by Hopkins Hatzopoulos et al. [5] with respect to SANS analysis showed that all hydrotopes (sodium p-n-alkylbenzoates, n=0-8) behaving as surfactant-like which has guided us to do theoretical investigations which might be helpful in illustrating such a phenomenon. In fact, the latter observation contradicts with the well-known assumption of that surfactant molecules must have chain of at least 8 carbon atoms in order to have self-assembled structure or following an “on-off” mode of aggregation. Table 1 lists the calculated theoretical parameters using DFT method for the presented compounds.

The results show no remarkable difference in head charge, tail charge, head surface area, charge on α-CH$_2$, polarizability of head, HOMO, LUMO for these hydrotopes. The reason for this may be attributed to the relatively low reactive side of the hydrocarboxonic alkyl chain as saturated group in contrast to the head group which remains fixed for all of the presented hydrotopes. In other words, these parameters have no influence on the cac values of amphiphilic molecules. It is clearly shown (Table 1) the head volume increased in zigzag mode with increasing the tail length. Such non-linear mode which represents the charge of number of methylene groups from odd to even is not new here. This is due to the observation that the zigzag mode was already found for some physical properties of hydrocarbons particularly those of alkynes. However, the increase in head volume may be attributed to that the negative charge of the head is enhanced by increasing the number of CH$_2$ groups as considered as electron donor group. On the other hand, the results indicate that the Log P values which represent the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium "octanol and water" increases with increasing tail length. For instance, compounds with high partition coefficients (high Log P) are preferentially distributed to hydrophobic compartment while hydrophilic compounds (low Log P) are preferentially found in the hydrophilic part. This can be attributed to the hydrophobic interactions through dispersion forces. On the other hand, the polarizability ($\alpha$) was also increased with the increasing the number of CH$_2$ groups at the tail because $\alpha$ depends on the induced dipole moment which is increased with increasing number of CH$_2$ groups according to the following relation [17], where ($\mu_{ind}$) is the induced dipole moment and (E) is the electric field strength.

$$\alpha=\frac{\mu_{ind}}{E} \left( \text{C}^2 \text{m}^2 \text{J}^{-1} \right)$$

(1)
Table 1. List of the calculated properties of the sodium p-n-alkylbenzoates (n=0-8) hydrotropes.

<table>
<thead>
<tr>
<th>Property</th>
<th>n = 0</th>
<th>n = 1</th>
<th>n = 2</th>
<th>n = 3</th>
<th>n = 4</th>
<th>n = 5</th>
<th>n = 6</th>
<th>n = 7</th>
<th>n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head Charge (e)</td>
<td>-0.765</td>
<td>-0.768</td>
<td>-0.768</td>
<td>-0.767</td>
<td>-0.765</td>
<td>-0.764</td>
<td>-0.767</td>
<td>-0.765</td>
<td></td>
</tr>
<tr>
<td>Tail Charge (e)</td>
<td>-0.338</td>
<td>-0.336</td>
<td>-0.340</td>
<td>-0.337</td>
<td>-0.339</td>
<td>-0.339</td>
<td>-0.337</td>
<td>-0.337</td>
<td></td>
</tr>
<tr>
<td>Charge $\alpha$-CH$_2$ (e)</td>
<td>non</td>
<td>-0.232</td>
<td>-0.224</td>
<td>-0.202</td>
<td>-0.206</td>
<td>-0.206</td>
<td>-0.206</td>
<td>-0.206</td>
<td></td>
</tr>
<tr>
<td>Head Surface area $\text{A}^2$</td>
<td>93.29</td>
<td>93.53</td>
<td>92.77</td>
<td>93.01</td>
<td>93.45</td>
<td>93.89</td>
<td>93.60</td>
<td>94.06</td>
<td>93.89</td>
</tr>
<tr>
<td>Tail surface area $\text{A}^2$</td>
<td>181.48</td>
<td>213.28</td>
<td>240.49</td>
<td>269.73</td>
<td>303.02</td>
<td>331.38</td>
<td>366.79</td>
<td>395.39</td>
<td>427.66</td>
</tr>
<tr>
<td>Total surface area $\text{A}^2$</td>
<td>274.77</td>
<td>301.82</td>
<td>328.13</td>
<td>357.89</td>
<td>392.11</td>
<td>420.22</td>
<td>456.62</td>
<td>484.38</td>
<td>517.21</td>
</tr>
<tr>
<td>Head Volume $\text{A}^3$</td>
<td>947.8</td>
<td>1110.2</td>
<td>1098.5</td>
<td>1173.0</td>
<td>1135.3</td>
<td>1326.5</td>
<td>1404.5</td>
<td>1478.7</td>
<td>1322.5</td>
</tr>
<tr>
<td>Tail Volume $\text{A}^3$</td>
<td>358.50</td>
<td>473.64</td>
<td>517.32</td>
<td>578.54</td>
<td>630.41</td>
<td>690.71</td>
<td>740.06</td>
<td>792.38</td>
<td>820.95</td>
</tr>
<tr>
<td>Total volume $\text{A}^3$</td>
<td>396.98</td>
<td>449.49</td>
<td>498.77</td>
<td>553.21</td>
<td>611.61</td>
<td>663.10</td>
<td>719.40</td>
<td>772.33</td>
<td>828.84</td>
</tr>
<tr>
<td>Chain length $\text{A}$</td>
<td>3.50</td>
<td>5.02</td>
<td>6.10</td>
<td>10.46</td>
<td>8.62</td>
<td>10.00</td>
<td>11.20</td>
<td>12.56</td>
<td>13.76</td>
</tr>
<tr>
<td>Polarizability of Head/ $\text{C}^2$ m$^2$ J$^{-1}$</td>
<td>3.842</td>
<td>3.842</td>
<td>3.842</td>
<td>3.842</td>
<td>3.842</td>
<td>3.842</td>
<td>3.842</td>
<td>3.842</td>
<td>3.842</td>
</tr>
<tr>
<td>Total polarizability $\text{C}^2$ m$^2$ J$^{-1}$</td>
<td>12.54</td>
<td>14.37</td>
<td>16.21</td>
<td>18.04</td>
<td>19.88</td>
<td>21.71</td>
<td>23.55</td>
<td>25.38</td>
<td>27.22</td>
</tr>
<tr>
<td>HOMO (eV)</td>
<td>-4.62</td>
<td>-4.62</td>
<td>-4.62</td>
<td>-4.63</td>
<td>-4.65</td>
<td>-4.64</td>
<td>-4.66</td>
<td>-4.66</td>
<td>-4.66</td>
</tr>
<tr>
<td>LUMO (eV)</td>
<td>3.93</td>
<td>3.84</td>
<td>3.84</td>
<td>3.83</td>
<td>3.77</td>
<td>3.81</td>
<td>3.75</td>
<td>3.80</td>
<td>3.74</td>
</tr>
<tr>
<td>$[\text{cac}][5]$</td>
<td>0.480</td>
<td>0.320</td>
<td>0.300</td>
<td>0.280</td>
<td>0.200</td>
<td>0.090</td>
<td>0.048</td>
<td>0.024</td>
<td>0.011</td>
</tr>
</tbody>
</table>
In order to find the best relationship between the calculated values of physical properties with the practical values of cac (Table 1), a general correlation matrix which gathers all calculated properties has been formed. Indeed, such a matrix will be quite helpful in order to verify if there is any combination between the calculated parameters. For example, the property of refractivity is derived directly from the polarizability which was therefore neglected from Table 1. This can be considered as an important point while concerning with building a multi-parametrical model. Interestingly, the results of constructed matrix show according to statistical parameters there is only one descriptor which is quite enough for predicting the cac of the presented hydrotropes as exhibited in Table 2. Indeed, this gives an efficient support to the previous experimental results [5, 6] as all the investigated sodium salts hydrotropes possess ‘on-off’ mode of association with no regards to hydrophobic chain length. This event may be explained in terms of the phenomenon that the presence of sodium carboxylate group as a polar head which could acts as an anti-hydrophobic effect. In other words, the water molecules surrounding this polar group will decrease the hydrogen bonding between each other which then reduce the density of solution [18]. Then, the movement of hydrotropes within solution will be much easier in this state as the shorter hydrophobic chain length will be more efficient in contrast to that of longer. This is because of the fact that the neighboring water molecules will be relatively close to hydrophobic part of shorter chain, while, the hydrophobic interactions of the longer chain length play the major role for aggregation. Thus, all of these hydrotropes behave as surfactant-like.

Hence, four properties have been chosen as a single descriptor for each developed model possessing good statistics stability and predictive power. One of these properties represents the electronic effect (polarizability of tail) and two representing the steric effect (tail volume and tail surface area). While the last one (log P of tail) is considered as a measure of the amount hydrophobicity which increases with increasing tail length (number of CH₂ groups) as illustrated above. Moreover, this parameter can be considered as hydrophilic-lipophilic balance of a substance which reflects its partitioning behavior between a polar (water) and non-polar (oil) medium. In fact, there is a clear physical meaning realized from all of these equations as the cac decreases with increasing the number of −CH₂− group. It should be noted that all of above selected descriptors are representing the properties of the hydrophobic group (tail) which is in good agreement with theory of micellization.

The results show that the amounts of the intercepts are more than the cac of the shorter chain length which give an indication for the successfullness of all suggested models. On the other hand, the relationship between the experimental and calculated cac values for these four models (Table 2) signifies an apparent weak point that resulted from the negative values of cac for the longer alkyl chain length (lower cac value), as shown clearly in Figure 1. Indeed, such a problem can be also realized from the value of standard error for the above model which exceeds the value of cac for the lower cac molecule. Therefore, the investigations should be extended for another suitable model. Such a problem may suggest there is no perfect linearity between cac versus the selected physical properties. Therefore, the relationship should be improved through using some mathematical operators such as square root, log, exponential, and so on. The results of such curve fitting treatments indicate that the logarithmic operator is the proper one which gives the best statistical stability and predictive power for the three properties TVO, PT and LPT as illustrated in Table 3.
Furthermore, the latter curve-fitting process has solved the problem of the negative value for those best three models as shown clearly in Figures 2-4. The parameters of cross validation correlation coefficient ($q^2$) and standard deviation of residual between observed and calculated values of cac have been introduced (Table 3) due to the apparent closeness in the values of statistical parameters ($r$ and S.E.) of these models. Indeed, the values of $q^2$ for these models are quite close to each other which they near to the top value (unity). However, the best model may be chosen with respect to the relatively best value of standard deviation between observed and fitted cac as given in Table 3. Hence, the model of polarizability of tail ([cac] = 1.52-1.09 log PT) is considered as the most powerful model for estimating the cac of the presented hydrotropes. In general, this model is quite significant from both of physical and statistical point of views.

**Table 2.** The best selected models obtained from the correlation matrix between cac and some of the calculated theoretical properties of hydrotropes with statistical parameters.

<table>
<thead>
<tr>
<th>Property</th>
<th>Symbol</th>
<th>Model ($y=a-bx$)</th>
<th>$r$</th>
<th>S.E. (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tail volume</td>
<td>TVO</td>
<td>[cac] = 0.840 -1.04x10$^{-3}$TVO</td>
<td>-0.988</td>
<td>0.032</td>
</tr>
<tr>
<td>Tail surface area</td>
<td>TSA</td>
<td>[cac] = 0.763 - 1.97x10$^{-3}$TSA</td>
<td>-0.972</td>
<td>0.040</td>
</tr>
<tr>
<td>Polarizability of tail</td>
<td>PT</td>
<td>[cac] = 0.714 -3.01x10$^{-2}$PT</td>
<td>-0.980</td>
<td>0.034</td>
</tr>
<tr>
<td>Log P of tail</td>
<td>LPT</td>
<td>[cac] = 0.687 - 0.141 LPT</td>
<td>-0.979</td>
<td>0.035</td>
</tr>
</tbody>
</table>

**Figure 1.** The relationship between experimental cac values and predicted cac of polarizability of tail (PT).
Table 3. The best selected models obtained from the treatment by curve-fitting for the relation between cac and some of the calculated theoretical properties of hydrotropes with statistical parameters.

<table>
<thead>
<tr>
<th>Property</th>
<th>Symbol</th>
<th>Model</th>
<th>$r$</th>
<th>S.E. (M)</th>
<th>$q^2$</th>
<th>SD (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tail volume</td>
<td>TVO</td>
<td>[cac] = 3.97-1.36 logTVO</td>
<td>-0.983</td>
<td>0.033</td>
<td>0.945</td>
<td>0.088</td>
</tr>
<tr>
<td>Polarizability of tail</td>
<td>PT</td>
<td>[cac] = 1.52-1.09 log PT</td>
<td>-0.981</td>
<td>0.033</td>
<td>0.943</td>
<td>0.026</td>
</tr>
<tr>
<td>Log P of tail</td>
<td>LPT</td>
<td>[cac] = 0.730-1.03 logLPT</td>
<td>-0.981</td>
<td>0.034</td>
<td>0.945</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Figure 2. Relationship between experimental cac and calculated cac values from the logarithm of tail volume.

Figure 3. Relationship between experimental cac and calculated cac values from the logarithm of polarizability of tail.
An application of the above selected three models for predicting critical micelle concentration (cmc) of two sets of different head groups of anionic surfactants was carried out as illustrated in Table 4. It is not surprising that the presented models are not applicable for estimating the cmc of ionic surfactants in contrast to cac of hydrotropes [19]. This can be attributed to the effect of presence of free gegen- or counter-ions which not exciting in hydrotropes systems. Furthermore, the presence of free gegen-ions could disturb the interactions between head groups which therefore deform the symmetry of micelle or aggregate system. Actually, the presence of these ions at Gouy-Gchapman layer [20] creates a real problem in computational investigations. This because the theoretical calculations estimate the properties of surfactant molecules in its monomer state as all these molecules are the same when they accumulated in micelle structure. It is apparent that the presented models are relatively more applicable for determining the cmc of sodium acetate micelle in contrast to that of sodium sulfate according to the values of statistical parameters as clearly shown in Table 4. This is because of the fact that the amount of free gegen-ions depends on the ionization of surfactant molecule. The relatively low ionization potential of sodium acetate surfactant decreases the probability of the presence of free gegen-ions in contrast to that of sodium sulfate. However, the values of standard deviation again suggest that the model of tail polarizability is relatively the best model for estimating the cmc of surfactants.
Table 4. Predicted $cmc$ for some surfactants using the three models of Table 3 versus experimental $cmc$.

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>$cmc^a$ [M]</th>
<th>TVO (Å$^3$) ${cmc}^b$ (Δ)$^c$</th>
<th>PT(C$^2$ m$^2$ J$^{-1}$) ${cmc}^d$ (Δ)$^c$</th>
<th>LPT ${cmc}^e$ (Δ)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium tetradeylsulfate</td>
<td>0.0021</td>
<td>1125.961</td>
<td>27.912</td>
<td>5.487</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.1800)</td>
<td>(-0.0559)</td>
<td>(-0.0315)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.1821)</td>
<td>(-0.058)</td>
<td>(-0.0336)</td>
</tr>
<tr>
<td>Sodium dodecylsulfate</td>
<td>0.0083</td>
<td>968.739</td>
<td>22.407</td>
<td>4.298</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.0912)</td>
<td>(0.0480)</td>
<td>(0.0777)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.0995)</td>
<td>(0.0397)</td>
<td>(0.0694)</td>
</tr>
<tr>
<td>Sodium decylsulfate</td>
<td>0.0330</td>
<td>860.835</td>
<td>18.737</td>
<td>3.506</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.0214)</td>
<td>(0.1327)</td>
<td>(0.1688)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.0544)</td>
<td>(0.0997)</td>
<td>(0.1358)</td>
</tr>
<tr>
<td>Sodium octylsulfate</td>
<td>0.1330</td>
<td>752.695</td>
<td>15.067</td>
<td>2.713</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.0577)</td>
<td>(0.2359)</td>
<td>(0.2835)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.0753)</td>
<td>(0.1029)</td>
<td>(0.1505)</td>
</tr>
<tr>
<td>SD</td>
<td>0.103</td>
<td>0.075</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>r$^2$</td>
<td>0.77</td>
<td>0.79</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Sodium octanoate</td>
<td>0.4000</td>
<td>609.929</td>
<td>13.232</td>
<td>2.562</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.1820)</td>
<td>(0.2974)</td>
<td>(0.3091)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.2180)</td>
<td>(-0.1026)</td>
<td>(-0.0909)</td>
</tr>
<tr>
<td>Sodium nonanoate</td>
<td>0.2100</td>
<td>667.713</td>
<td>16.419</td>
<td>3.030</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.1285)</td>
<td>(0.1952)</td>
<td>(0.2341)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.0815)</td>
<td>(-0.0148)</td>
<td>(0.0241)</td>
</tr>
<tr>
<td>Sodium decanoate</td>
<td>0.1090</td>
<td>721.698</td>
<td>18.254</td>
<td>3.426</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.0826)</td>
<td>(0.1451)</td>
<td>(0.1791)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.0264)</td>
<td>(0.0361)</td>
<td>(0.0701)</td>
</tr>
<tr>
<td>Sodium dodecanoate</td>
<td>0.0278</td>
<td>828.746</td>
<td>21.924</td>
<td>4.218</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.0009)</td>
<td>(0.0583)</td>
<td>0.0861</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.0269)</td>
<td>(0.0305)</td>
<td>(0.0583)</td>
</tr>
<tr>
<td>SD</td>
<td>0.088</td>
<td>0.046</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>r$^2$</td>
<td>0.91</td>
<td>0.98</td>
<td>0.94</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Experimental $cmc$ taken from Ref. 16, $^b$ calculated using this Eq. $\lbrack cac \rbrack = 3.97-1.36 \log \text{TV0}$, $^c$ $\Delta = cmc$ (calculated,)$-cmc$ (experimental), $^d$ calculated using this Eq. $\lbrack cac \rbrack = 1.52-1.09 \log \text{PT}$, $^e$ calculated using this Eq. $\lbrack cac \rbrack = 0.730-1.03 \log \text{LPT}$, $^f$ Standard deviation.
Conclusions

On the basis of our results, one could conclude that there are good models which are statistically significant have been developed for estimating the cac of hydrotropes. In addition, the obtained results have supported the recent reports of Hatzopoulos et al. [5, 6] reflecting that all hydrotropes could act as a surfactant. It is not possible to apply a unique model for all kinds of hydrotropes and surfactants due to the change in the head group interactions in addition to gegen-ions effect. The results suggest that the estimation of cac or cmc for amphiphilic molecules using computational chemistry tools is quite possible. Finally, theoretical calculations based on density functional theory can be considered as a powerful tool for estimation the physical properties of amphiphilic molecules.

References


