Experimental, Theoretical and Biological Activity Study on the Acyl-Substituted Benzo-18-crown-6, Dibenzo-18-crown-6 and Dibenzo-24-crown-8

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Abstract

Hexadecanoyl, dihexadecanoyl, dioctadecaneoyl, di-10-undecenoyl, and dicis-9-octadecenoyl derivatives of benzo[18]crown-6, dibenzo[18]crown-6 and dibenzo[24]-8 were synthesized by the condensation of carboxylic acids (palmitic, stearic, oleic and undecenoic acid) with benzo and dibenzo crown ethers in the presence of zinc chloride. The extraction equilibrium constants of such macrocyclic ethers with long side chains were estimated using chloroform/water and dichloromethane/water membranes transfer of Na-PAR (4-(2-pyridylazo)-resorcinol mono sodium monohydrate) with UV–Vis spectroscopy. It was found that they were in the range of 10.88–11.71 in dichloromethane and 8.04–11.77 in chloroform. These results actually show that the Na+ binding effect of macrocyclic ethers depends on the type and the length of side chains. The geometrical properties of the molecules were studied employing semi-empirical calculations by simulated annealing technique. The frontier molecular orbital energies and dipole moments were also examined. The biological activity results showed that the synthesized crown ethers have no activity against the studied microorganisms.

Introduction

Cation and anion recognition of macrocyclic ethers have been known widely [1, 2]. Selective ion binding is utilized to transfer alkaline and alkaline earth metals in a liquid/liquid membrane system [3, 4]. Such behaviors of the various macrocyclic ethers have been investigated and results have showed the effect of macrocyclic size as well as the incorporating groups in the moiety [5–7]. Accordingly, several membrane systems displaying the mobility of the cations in the presence of macrocyclic ethers have been reported.

The synthesis and estimation of cation-binding role of macrocyclic ethers, studied with extraction equilibrium constants of macrocyclic ethers, are a well-known procedure displaying selective membrane transfer ability of macrocyclic ligands for any type of a cation [1–8]. The discovery of crown compounds, with unusual cation binding properties promoted the work of selective transport of metals in large-scale processes, as well as in the biological systems [3–7]. However, in such processes function of the anion, effective ionic radius, coordination numbers, charge densities, charge distributions and hydration are involved, preferably large type of anion structures were utilized for the maximum delocalization for the ion pair formation [2, 3].

The synthesis and the utility of crown ethers with carbon pivot chains, called lariat ethers, have opened another area for ion transport studies [4, 9]. Several types of crown ethers with chromophores side arms were synthesized and characterized with ion pair extraction methods [7, 9]. Introduction of polyethylene glycol side chains as a crown ether moiety and investigation of stability constants of such lariat ethers were well studied [4, 8]. However, the effects of side arm length have not so marked well up to now.

Hence, we choose three macrocycles (Benzo-18-crown-6, Dibenzo-18-crown-6 and Dibenzo-24-crown-8), the widely used crown ethers in the literature, to investigate the effect of acyl group substitution on their complexation ability with Na-PAR. In addition to that, their molecular properties were of special interest with the computational efforts.

On the other hand, many studies on the antibacterial activity of the fatty acids have been published in the literature and McGaw *et al*. [10] reviewed them in 2002.

Recently, Kilic *et al*. [11] have found that the seed extracts including fatty acids of *Salvia* species,

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S. braceata and *S. aethiopis*, shows good activity against *S. aureus*, *E. coli*, *M. smegmatis*, and *C. albicans* microorganisms. Therefore, the synthesized acyl-substituted crown ether derivatives were evaluated in accordance with their antimicrobial activity at the final part of the study.

Experimental

General

Melting and boiling points are uncorrected. Benzo-18-crown-6, dibenzo-18-crown-6 and dibenzo-24-crown-8 were synthesized according to Pedersen as we reported recently [1, 2]. 4-(2-Pyridylazo)-resorcinol monosodium monohydrate salt, (Na-PAR), (ALDRICH) was dried at 0.10 torr on P_2O_5 for 48 h. Carboxylic acids: palmitic, stearic, oleic and undecenoic acids, polyphosphoric acid (PPA) and $ZnCl_2$ were from ALDRICH. The IR (KBr) was obtained from Perkin Elmer model BX 2 FTIR. 400 MHz ^{1}H-NMR in $CHCl_3$/TMS was measured with BRUKER Spectrometer, model AVANCE DPX-400. The compounds **2a**, **2b** gave molecular peaks of low abundance while compounds **2c–2h** gave no such evidence, instead of complicated fragmentation pattern.

Organic Syntheses

n-Hexadecanoylbenzo-18-crown-6 (2a)
Benzo-18-crown-6 (0.75 g, 2.4 mmol), palmitic acid (0.614 g, 2.4 mmol), $ZnCl_2$ (0.33 g, 2.4 mmol) placed in a flask (150 ml) under a reflux condenser were heated at 135–140 °C for 2 h. HCl (1 N, 100 ml) was added to cool reaction mixture and boiled for 5–10 min. Solid product was filtered, dried and recrystallized from benzene. Powder crystals (**2a**), 0.20 g, and 15% yield. mp 51.4 °C; IR (KBr), 3080, 3030, 2940, 2870, 2855, 1800, 1750, 1731, 1710, 1640, 1470, 1465, 1180 cm^{-1}; ^{1}H-NMR (CDCl$_3$/TMS, 400 MHz) δ ppm 0.90(3H,t,CH$_3$), 1.86 (26H,m,CH$_2$), 2.81(4H,t,CH$_2$CO), 3.63(4H,s,CH$_2$O), 3.72(8H,m,CH$_2$O), 4.03(4H,t,CH$_2$O), 4.24(4H,t,CH$_2$O), 6.98 (H,d,Ar), 7.50(H,d,Ar), 7.62 (H,m.Ar).

Bis-(di-n-hexadecanoyl)dibenzo-18-crown-6 (2b)
Dibenzo-18-crown-6 (1.8 g, 5.0 mmol), palmitic acid (C$_{15}$H$_{31}$COOH) (5.12 g, 20 mmol) and PPA (25 g, ×mmol) were refluxed in flask (150 ml) at 110–120 °C for 1 h. Raw mixture was boiled with water (100 ml) for 5–10 min then cooled and extracted with CH$_2$Cl$_2$. Oily raw product obtained upon evaporation of solvent was chromatographed on basic alumina (Fluka) with CH$_2$Cl$_2$. Colorless oil, (**2b**), 0.92 g, 22% yield; IR (KBr) 3080, 2940, 2870, 2840, 1750, 1710, 1640 cm^{-1}; ^{1}H-NMR (CDCl$_3$/TMS 400 MHz) δ ppm 0.88(6H,t,CH$_3$), 1.38(4H,t,CH$_2$), 1.65(52H,m,CH$_2$), 2.40(6H,m,CH$_2$), 3.88(8H,t,CH$_2$O), 4.19(8H,t,CH$_2$O), 7,28(2H,d,Ar), 7.30(2H,d,Ar), 7.40(2H,s,Ar).

Bis-(di-n-octadecanoyl)dibenzo-18-crown-6 (2c)
Dibenzo-18-crown-6 (1.8 g, 5.0 mmol), stearic acid (2.84 g, 1.0 mmol) and $ZnCl_2$ (1.36 g, 1.0 mmol) were heated at 135–140 °C for 2 h in a flask (250 ml) under a reflux condensor. Cooled mixture were treated with HCl (100 ml, 0.1 N) and boiled for 5–10 min. Precipitated raw product was filtered, dried recrystallized from ether. Colorless crystals (**2c**), mp 102 °C, 0.714 g, 16% yield; IR (KBr) 3030, 2940, 2920, 2855, 2835, 1750, 1731, 1700, 1620, 1585, 1565, 1515, 1470, 1080 cm^{-1}; ^{1}H-NMR(CDCl$_3$/TMS, 400 MHz) δ ppm 0.89(6H,t,CH$_3$), 1.30(60H,m,2C$_{15}$H$_{30}$), 2.75(4H,t,CH$_2$CO), 3.88 (8H,t,CH$_2$O), 4.19(8H,t,CH$_2$O), 7.20(2H,d,Ar), 7.28 (2H,d,Ar), 7.30(2H,s,Ar).

Bis-(di-10-undecenoyl)dibenzo-18-crown-6 (2d)
Dibenzo-18-crown-6 (1.8 g, 5.0 mmol), 10-undecenoic acid (1.84 g, 10 mmol) and $ZnCl_2$ (1.36 g, 10 mmol) were refluxed in a flask (150 ml) at 135–140 °C for 2 h. The cooled mixture was acidified with HCl (100 ml, 0.1 N) and heated for 5–10 min. Raw product was chromatographed from alumina with CH$_2$Cl$_2$. Oil, (**2d**), 0.346 g, 10% yield, IR (KBr) 3100, 3030, 2870, 2940, 1800, 1790, 1735, 1640, 1625, 1575, 1515, 1470, 1280, 1170, 1025, 795, 680 cm^{-1}; ^{1}H-NMR (CDCl$_3$/TMS, 400 MHz) δ ppm 0.80(6H,t,CH$_3$), 1.35(32H,m,CH$_2$), 2.78(4H,t,CH$_2$CO), 3.80(8H,t,CH$_2$O), 4.10(8H,t.CH$_2$O), 5.70(4H,m,4CH) 6.85(2H,d,Ar), 7.10(2H,d,Ar), 7.90(2H,m,Ar).

Bis-(dioctadecene-9-oyl)dibenzo-18-crown-6 (2e)
Dibenzo-18-crown-6 (1.8 g, 5 mmol), oleic acid (2.82 g, 10 mmol) $ZnCl_2$ (1.36 g, 10 mmol) were refluxed in a flask (150 ml) at 135–140 °C for 2 h. The cooled mixture was acidified with HCl (100 ml, 0.1 N) and heated for 5–10 min. Raw product was chromatographed from alumina with CH$_2$Cl$_2$. Oil, (**2e**), 0.622 g, 14% yield, IR (KBr), 3080, 3030, 2940, 2870, 1800, 1750, 1731, 1710, 1640, 1470, 1465, 1160 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm 0.90(6H,t,CH$_3$), (56H,m,CH$_2$), 2.67(4H,t,CH$_2$CO). 3.82(8H,t,CH$_2$O), 4.12(8H,t,CH$_2$O), 5.65(4H,m,4CH) 6.82(2H,d,Ar), 7.09(2H,d,Ar), 7.89 (2H,m,Ar).

Bis-(dihexadecanoyl)dibenzo-24-crown-8 (2f)
Dibenzo-24-crown-8 (1.12 g, 2.5 mmol), palmitic acid (1.28 g, 5.0 mmol) and $ZnCl_2$ (0.68 g, 5 mmol) were refluxed in a flask (150 ml) at 135–140 °C for 2 h. The cooled mixture was acidified with HCl (100 ml, 0.1 N) and heated for 5–10 min. Solid raw product was filtered and dried then recrystallized from benzene. Colorless crystals, (**2f**), 0.35 g, 15% yield, mp 61 °C. IR (KBr), 3080, 2940, 1800, 1625, 1575, 1720, 1665, 1470, 1465, 1160, 1030, 780 cm^{-1}; ^{1}H-NMR(CDCl$_3$, 400 MHz) δ ppm 0.89(6H,t,CH$_3$), 1.39(4H,m,CH$_2$), 1.69(48H,m,CH$_2$), 2.80(4H,t,CH$_2$CO), 3.81(8H,s,CH$_2$O), 3.94(8H,t,CH$_2$O), 4.32(8H,t,CH$_2$O), 6.86(2H,d,Ar), 7.11(2H,d,Ar), 7.91 (2H,m,Ar).

Table 1. The Na-PAR extraction equilibrium constants with benzo−18-crown−6, dibenzo−18-crown−6 and dibenzo−24-crown−8 crown ether derivatives, (**2a–2h**), at 25 °C

Solvent	ε^{20}	Value	Crown ether									
			NCr	Cr	2a	2b	2c	2d	2e	2f	2g	2h
CH$_2$Cl$_2$	9.08	Log K_{ext}		12.49 ± 1.64	11.39 ± 0.51	11.71 ± 0.85	11.37 ± 0.88	11.48 ± 0.88	10.88 ± 0.98	11.12 ± 1.79	11.29 ± 1.04	11.28 ± 1.24
		K_D	1.12	29.90 ± 0.17	11.17 ± 0.12	14.62 ± 0.07	5.28 ± 0.1	13.34 ± 0.08	7.89 ± 0.09	9.80 ± 0.11	10.61 ± 0.11	10.53 ± 0.12
CHCl$_3$	4.81	Log K_{ext}		9.62 ± 1.23	11.38 ± 0.79	11.77 ± 0.77	8.04 ± 0.60	9.54 ± 0.35	8.79 ± 0.49	8.89 ± 0.98	9.24 ± 0.94	10.29 ± 0.78
		K_D	1.47	2.40 ± 0.04	32.44 ± 0.20	62.03 ± 0.31	0.54 ± 0.02	6.64 ± 0.04	1.92 ± 0.03	3.12 ± 0.03	5.45 ± 0.03	8.24 ± 0.06

Corr. coefficient, 1.000; NCr, no crown ether in solution; Cr: Dibenzo-18-crown-6 crown ether.

K_D, a distribution constant of sodium ion between water and organic solvent.

*Bis-(dioctadecanoyl)dibenzo-24-crown-8 (**2g**)*

Dibenzo-24-crown-8 (2.5 mmol, 1.12 g), stearic acid (1.42 g, 5 mmol) and ZnCl$_2$ (5 mmol, 0.68 g) were refluxed in a flask (150 ml) at 135–140 °C for 2 h. The cooled mixture was acidified with HCl (100 ml, 0.1 N) and heated for 5–10 min. Solid raw product was filtered and dried then recrystallized from ether. Colorless crystals, (**2g**), 0441 g, 18% yield, mp 52 °C; IR (KBr), 3030, 2940, 2920, 1720, 1700, 1665, 1455, 1180, 790 cm^{-1}; ^{1}H-NMR(CDCl$_3$/TMS 400 MHz) δ ppm 0.91(6H,t,CH$_3$), 1.30(60H,m,CH$_2$), 2.80(4H,t,CH$_2$CO), 3.94(8H,t,CH$_2$O), 4.32(8H,t,CH$_2$O), 6.86(2H,d,Ar), 7.11 (2H,d,Ar), 7.91(2H,m,Ar).

*Bis-(di-10-undecenoyl)dibenzo-24-crown-8 (**2h**)*

Dibenzo-24-crown-8 (1.12 g, 2.25 mmol), oleic acid (C$_{17}$H$_{33}$COOH) (1.41 g, 5 mmol) and ZnCl$_2$ (0.68 g, 5 mmol) were refluxed in a flask (150 ml) at 135–140 °C for 2 h. The cooled mixture was acidified with HCl (100 ml, 0.1 N) and heated for 5–10 min. Solid raw product was filtered and dried then recrystallized from benzene. Colorless crystals, (**2h**), 0.29 g, 12% yield. mp. 48.5 °C; IR (KBr), 3100, 3080, 2940, 2870, 2850, 1800, 1745, 1720, 1701, 1665, 1640, 1575, 1470, 1170 cm^{-1}; ^{1}H-NMR(CDCl$_3$/TMS 400 MHz) δ ppm 0.86(6H,t,CH$_3$), 1.39(32H,m,CH$_2$), 2.82(4H,t,CH$_2$CO), 3.95(8H,t,CH$_2$O), 4.33(8H,t,CH$_2$O), 6.86(2H,d,Ar), 7.11(2H,d,Ar), 7.91 (2H,m,Ar).

Determination of extraction association constants and dispersion constants

In the present work, the extraction process of cations was conducted in a glass reactor (100 ml) equipped with a mechanical stirrer as 25 ml portions of water/organic solvents, (CH$_2$Cl$_2$ and CHCl$_3$), containing crown ethers at 25 °C. Each aliquot, (10 ml), was stirred for 2 h with the optimized macrocyclic ligand concentrations, mol/l (4 × 10^{-5}, 40 × 10^{-5}, 80 × 10^{-5}, 200 × 10^{-5}, 250 × 10^{-5}) and equivalent amount of Na-PAR solutions (pH = 6.1–6.7) then allowed to stand for 30 min to complete the phase separation. The concentrations of Na-PAR in the aqueous phases were determined spectrophotometrically (Varian Cary model 1E UV-visible spectrophotometer) at 407 nm with appropriate quartz cells 2–50 mm in length. Each absorbance value was the average of three

subsequent measurements. The results are displayed as Log K_{ext} with experimental errors (± 2.00), in Table 1 [12].
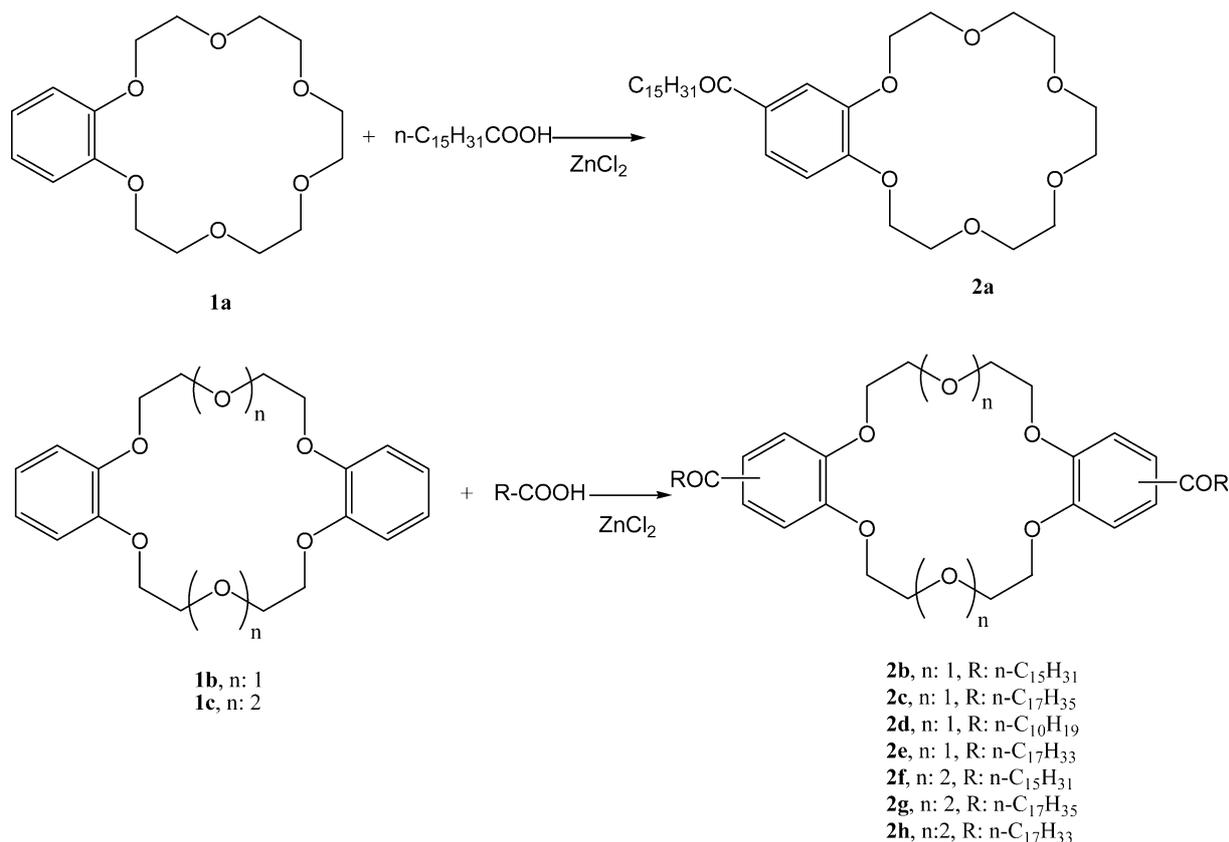
Experimental results and discussions

In the present work, the acyl and bis-acyl substituted benzo-18-crown-6, dibenzo-18-crown-6 and dibenzo-24-crown-8 derivatives of hexadecanoylbenzo-18-crown-6 (**2a**), bis-dihexadecanoyldibenzo-18-crown-6 (**2b**), bis-dioctadecanoyldibenzo-18-crown-6 (**2c**), bis-di-10-undecenoyldibenzo-18-crown-6 (**2d**), bis-di-9-octadecenoyldibenzo-18-crown-6 (**2e**), bis-dihexadecanoyldibenzo-24-crown-8 (**2f**), bis-dioctadecanoyldibenzo-24-crown-8 (**2g**) and bis-9-octadecenenoyldibenzo-18-crown-6 (**2h**), were synthesized using carboxylic acids, in the presence of polyphosphoric acid (PPA) and ZnCl$_2$ (Scheme 1).

An anionic color compound of Na-PAR, in Scheme 2, was used to follow the cation transport process using UV–VIS spectrometry [13–17]. The large and strong chromophore anion of the guest metal, Na$^+$ was readily mobilized by the macrocyclic ethers [5–7] in CHCl$_3$/water and CH$_2$Cl$_2$/water membranes.

Reports and reviews in this area showed the cation transport role of crown ethers depending on the organic solvent/water bilayer systems as well as the type and size of crown ethers and their side groups [7–9, 13–15]. In this technique, a cation is paired with a chromophore anion dissolved in water. The spectrophotometric methods for solvent extractions of an ion association complex and a chromophore anion have been commonly used [3–5, 13–16]. Therefore, the thermodynamic properties of crown ether derivatives were revealed with the comprehension of the other analytical methods for stability of the cation-crown ether complexes in different solvents [17–24].

We studied in the present work with a common formalism of Equations (1–3), which is almost the same as those described in a previous paper [12, 21–23], so it is stated briefly below. The equilibrium processes taking place during the extraction between an aqueous solution containing the alkali metal cation, M$^+$(w), and organic anion, A$^-$(w), and an organic solution containing crown ethers L(org), can be written as:
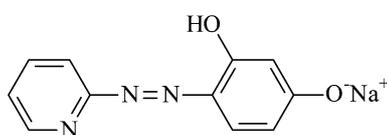
Scheme 1.

$$M^{m+}_{(aq)} + L_{(org)} + mA^-_{(aq)} \overset{K_{ext}}{\rightleftharpoons} (MLA_m)_{(org)} \quad (1)$$
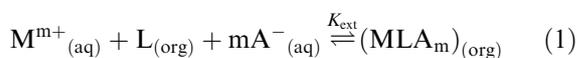
$$K_{ext} = \frac{[MLA_m]_{(org)}}{[M^{m+}]_{(aq)}[L]_{(org)}[A^-]^m_{(aq)}} \quad (2)$$

$$K_D = \frac{[MLA_m]_{org}}{[M^{m+}]_{aq}} \quad (3)$$

K_{ext} is extraction equilibrium constant; $[M^{m+}]$ and $[MLA_m]$ are the concentrations of metal cation in aqueous phase and organic phase, respectively. K_D denotes a distribution constant of ligand between organic solvent and water. Both are determined spectrophotometrically as described in experimental part.

The results of Log K_{ext}, in our work as shown in Table 1 are rather similar, and the side arms are not seem to be selective to mobilize the Na$^+$ cation into the

Na-PAR

Scheme 2.

organic phase although the side arms serve as a lipophilic component, thereby increasing the solubility of the side armed crown ethers in nonpolar solvents. Moreover, the organic solvents, which solubilize the aromatic body effectively, do not sense the aliphatic side chains any more. However, Log K_{ext} values are rather selective in CHCl$_3$ that are, although, larger in CH$_2$Cl$_2$ compared to CHCl$_3$. In general, except for the case of **2e** ligand in CH$_2$Cl$_2$ and **2c**, **2e** and **2h** ligands in CHCl$_3$, in six oxygen member rings are more effective than the eight oxygen member ring crowns to mobilize the Na$^+$ that indicates the role of ionic radii upon the size of crown ether for complex formation [1–6]. On the other hand the Log K_{ext} value of **2b** ligand is found slightly larger than the others, and the Log K_{ext} values for the same solvent are approximately equal, regardless of the nature of the central sodium metal ion, resulting in the fact that no large difference is found among the Log K_{ext} values.

As examined K_D values given in Table 1, it can be revealed that two molecules, **2a** and **2b**, which has the acyl substituent, –C$_{15}$H$_{31}$ group, have higher values, 32.44 and 62.03, respectively. This means that the cavity and shape of these molecules are suitable for the binding and mobility of Na$^+$ cation. To answer the question why **2a** and **2b** molecules have higher values, we have carried out theoretical calculations at semi-empirical level and explored the molecular structure of the complexed and uncomplexed crown ethers.

Computational results and discussions

Various quantum-chemical and force-field calculations of crown ethers and of their metal cation complexes have been reported [25–28], even on the *ab initio* level [29, 30] and DFT level [31, 32]. As usual for flexible molecules of this size, a large number of conformers will be obtained by using these methods. In order to establish the preferred conformers of lowest energy for the unsubstituted and substituted benzo-18-crown-6, dibenzo-18-crown-6 and dibenzo-24-crown-8, the simulated annealing technique was employed [33].

For these computations, a simulation protocol involving a heating time of 0.1 ps, followed by a 1 ps simulation at 3000 K and cooling to 298 K within 100 ps was applied on initially geometry optimized structures at PM3 self-consistent field molecular orbital level, which is generally satisfactory, especially
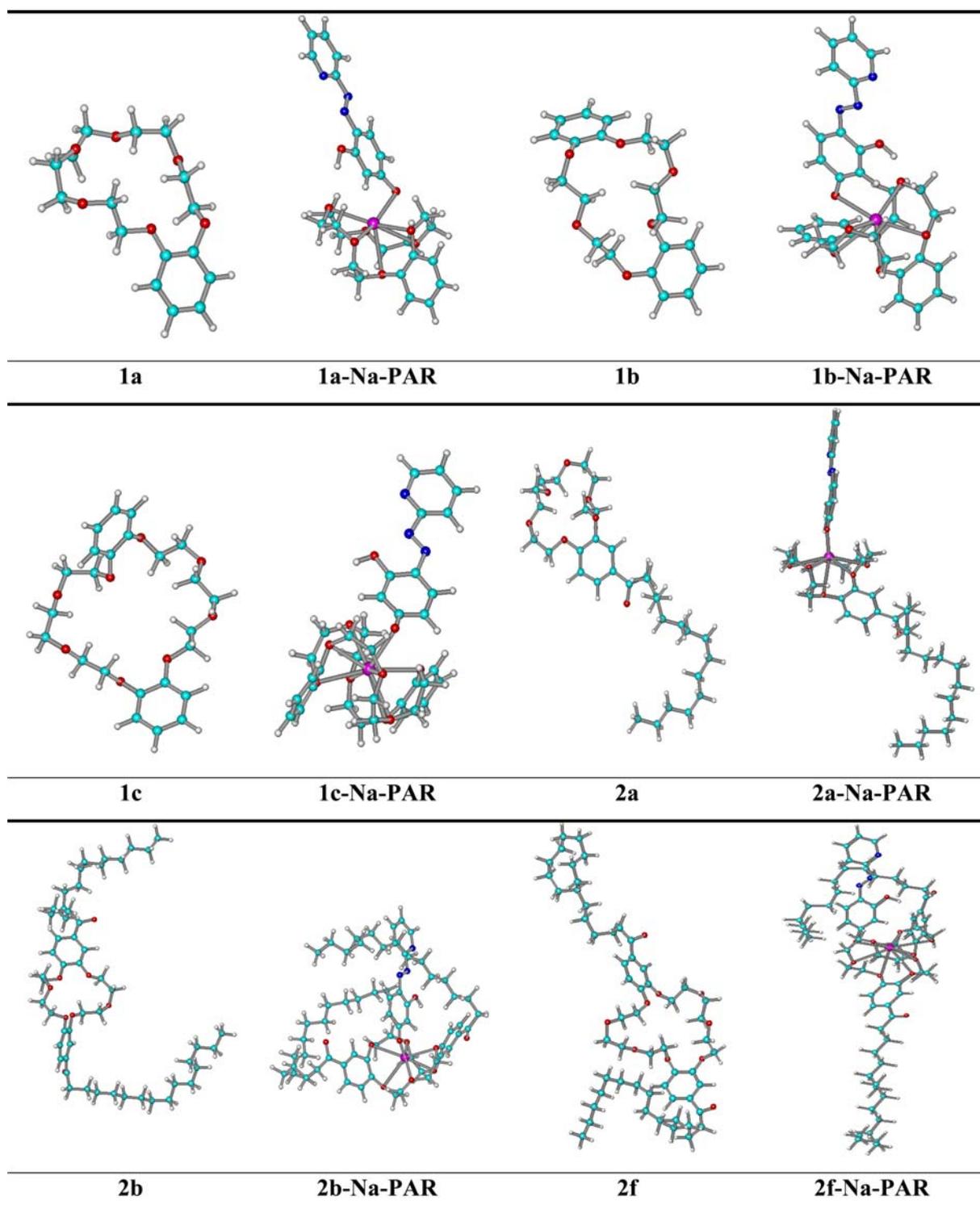

Figure 1. Optimized structures of free and Na-PAR complexed crown ethers by using simulated annealing technique.

considering the computing time required [34]. The time step of 0.5 fs was used for molecular dynamic studies. Energies were refined by using ZINDO/1 level [35]. All these calculations were performed by using Hyperchem 7.5 program.

The obtained geometries of free and Na-PAR complexed crown ethers, **1a**, **1b**, **1c**, **2a**, **2b** and **2f** were given in Figure 1. The acyl substitution on crown ethers do not exhibit large variations from the unsubstituted crown ethers, whereas they gain the polarity as can be understood from the dipole moment values given in Table 2. As the dipole moments reflect the charge distribution they can be used as descriptors to depict the charge movement across the molecule between the uncomplexed crown ether and complexed crown ether. The total computed dipole moments for the free crown ethers are 2.980–15.987 D and that for the complexed crown ethers are 9.095–17.743 D by ZINDO/1 calculations. The differences between the complexed and uncomplexed crown ether are 12.136, 10.101, 14.763, 4.707, 10.001, and −2.906 D for **1b**, **1c**, **2a**, **2b** and **2f**, respectively, the dipole moment being larger in the case of the complexed crown ethers except only **2f**. This reflects the fact that there is a significant charge transfer between the two states, which facilitates the charge separation process (and thus leads to enhanced fluorescent quantum yield).

On the other hand, likewise the organic anion of PAR is well hydrogen bonded to the crown ether part with the O–H hydrogen bond on the large organic counter ion. As it is apparent in Figure 1, the Na-PAR complexed crown ethers with all oxygen electron pairs pointing inwards also provides an ideal cavity for the guest molecule. Thus, a solution of these crown ethers in polar organic solvents, such as CH_2Cl_2, $CHCl_3$ has given much more dye extraction than other crown compounds and solvents [23].

The highest occupied molecular orbital (HOMO) and lowest occupied molecular orbital (LUMO) energy as well as their differences (the interfrontier energy gap) are shown in Table 2. As Table 2 reveals the LUMO and ΔE values for the free crown ethers are higher than that for the complexed crown ethers. The HOMO and LUMO energy schemes can be seen in Figure 2 for **3a + Na-PAR**. Note that in all Na-PAR complexed structures, Na-PAR ligand contributes to the HOMO orbital, whereas, the contribution to the LUMO orbital is observed from crown ether part.

Biological assessments

The synthesized crown ethers, **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, and **2h**, were tested against standard bacterial strains; *E. coli* ATCC 29998, *S. epidermidis* ATCC 12228, *B. subtilis* ATCC 6633, *S. aureus* 6538 P, *S. typhimirum* CCM 583, *K. pneumonia* CCM 2318, *P. aeruginosa* ATCC 27853, *E. feacalis* ATCC 29212 and a fungi *C. albicans* ATCC 10239. Disc diffusion method was applied for the determination of antimicrobial activities of the samples (NCCLS, 2000). Extracts were dissolved in dimethyl sulfoxide (DMSO) and then filter-sterilized using a 0.20-μm membrane filter. A suspension of the tested microorganism (0.1 ml of 10^8 cells/ml) was spread over the surface of agar plates (MHA and SDA). Filter papers having a diameter of 6 mm, soaked with 10 μl of extract samples and 8 μl of essential oils were placed on the inoculated agar plates. Before incubation all Petri dishes were kept in the refrigerator (4 °C) for 2 h. Then they were incubated at 37 °C for 24 h for bacteria and at 30 °C for 48 h for the yeasts. The diameters of the inhibition zones were measured in millimeters [24]. Unfortunately, the synthesized crown ethers do not show any biological activity against the studied microorganisms.
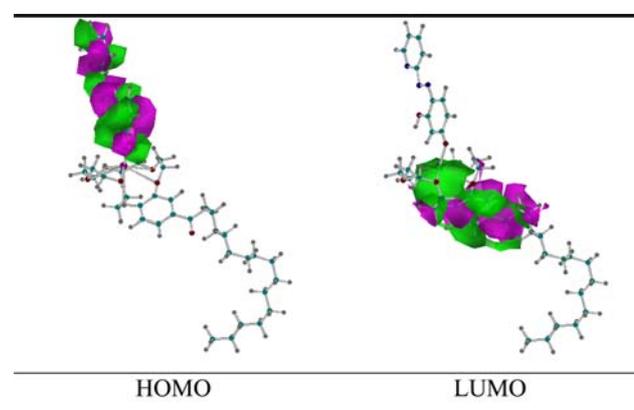

Figure 2. HOMO-LUMO schemes of **2a + Na-PAR**.

Table 2. The FMO energies, interfrontier energy gaps, dipole moments and dipole moments gaps of the free and Na-PAR complexed crown ethers (energies in eV and dipole moment in Debyes)

Free/complexed	E_{HOMO}	E_{LUMO}	ΔE^{a}	Dipole moment	ΔD^{b}
1a/(1a + Na-PAR)	−7.51/−3.39	7.80/6.10	15.31/9.49	4.490/16.626	12.136
1b/(1b + Na-PAR)	−7.41/−3.50	7.75/5.82	15.16/9.32	3.553/13.654	10.101
1c/(1c + Na-PAR)	−7.28/−3.10	7.74/6.12	15.02/9.22	2.980/17.743	14.763
2a/(2a + Na-PAR)	−6.28/−3.75	7.04/5.16	13.32/8.91	4.388/9.095	4.707
2b/(2b + Na-PAR)	−7.07/−3.44	6.02/5.27	13.09/8.71	7.015/17.016	10.001
2f/(2f + Na-PAR)	−6.06/−3.60	7.07/5.24	13.13/8.84	15.987/13.081	−2.906

[a]$\Delta E = E_{LUMO} - E_{HOMO}.$
[b]$\Delta D = D$(complexed CE) − D(free CE).

Conclusions

In this paper we described the synthesis of the acyl-substituted benzo-18-crown-6, dibenzo-18-crown-6 and dibenzo-24-crown-8 and their complexation properties. This complexation work has shown firstly that CH_2Cl_2 is found to be better than $CHCl_3$ as an extractive solvent for these synthesized molecules. Two of them, **2a** and **2b**, shows the high mobility values for Na^+ cation from water phase to organic phase with high K_D values. From the theoretical calculations, Na-PAR complexed crown ethers with all oxygen electron pairs pointing inwards provide an ideal cavity for the guest molecule. The optimized structure also reveal that the acyl substituents encircle Na-PAR ligand efficiently and prevent the complexed crown ethers from the interaction with water phase. Therefore, the arene group on macro ring has profound effect on cavity size and the structure of side arm has effect on complexation of crown ether.

Moreover, the synthesized crown ethers were tested for biological activity. However, there were no activities observed against the studied microorganisms. For the future study considered, the carbonyl groups of the acyl-substituted crown ethers, **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g** and **2h**, will be easily converted to the functional groups, $-NH_2$, $-SO_3$, $-OH$ etc. Hence, these changes will affect the complexation and biological activity of the molecules.

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