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Synthesis of new indolyl crown ethers catalyzed with ferric hydrogensulfate

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Abstract

Efficient reaction of bis-indolyl podand with different aldehydes using $Fe(HSO_4)_3$ as catalyst to afford the corresponding new indolyl crown ethers is described. The structures of three distinct isomers have been optimized using HyperChem geometry optimizations. Also percentage of each isomer was obtained with ^1H NMR spectroscopy.

Keywords: Ferric hydrogensulfate; Bis-indolyl podand; Indolyl crown ether; $Fe(HSO_4)_3$

Crown ethers are heteromacrocycles in which the framework is typically comprised of repeating ethylene oxy units. Nitrogen and sulfur commonly replace oxygen in this framework leading to a great variety of compounds that have been used in molecular recognition studies and supramolecular chemistry [1–4]. Alkali metal cation–*p* interactions have recently received considerable attention due to their biological importance [5–9]. There has been much progress in the computational approaches in supramolecular chemistry, which may lead to the microscopic insight into the structural and thermodynamical features involved in the processes of molecular recognition and supramolecular organization [10–15]. Great progress for computational facilities provides us an opportunity to study the relatively large and complicated supramolecular system. In this work, we have synthesized some new indolyl crown ethers and have studied the structures and energies of their conformers.

1. Results and discussion

Bis-indolyl podand **2** was obtained in high yield by alkylation of 2-methyl indole **1** with triethylene glycol ditosylate in the presence of KOH in DMF at room temperature. New bis-indolyl crown ethers have been synthesized *via* $Fe(HSO_4)_3$ (10 mol%) catalyzed condensation of bis-indolyl podand **2** (1 equiv.) and aldehyde (1 equiv.) under mild conditions (Scheme 1). The reaction is facile and complete within 60 min at room temperature. The structural assignments of compounds **3a–e** were determined based on the analytical and spectral data. In the ^1H NMR spectrum of **3e** the three signals at 5.98, 6.08 and 6.17 ppm assignable to benzyl protons were attributed to three isomers of **3e**.

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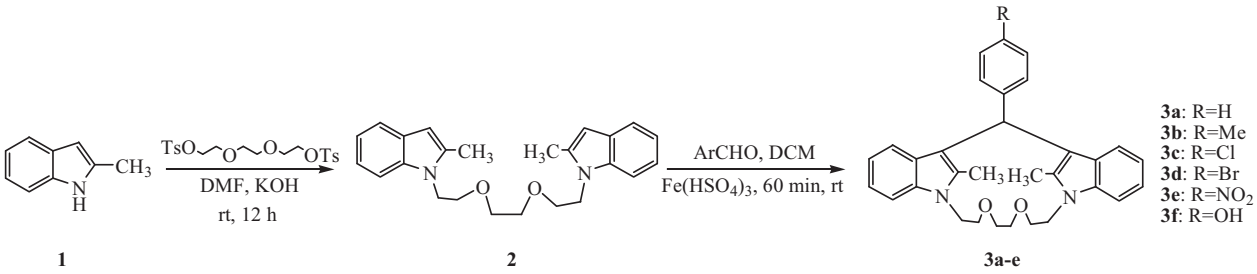

Scheme 1. Synthesis of indolyl crown ethers.

This observation is clearly approved that all three isomers are converted to each other slowly and the chemical moieties are different for their benzyl protons. One of the main reasons for slow conversion in three isomers of compounds **3a**–**e**, can be related to the methyl groups in 2-methyl indole rings. These isomeric relationships were not reported in similar reaction with indole [16].

Fig. 1 shows three isomers of compound **3a**. As it is cleared, there are two isomers in *syn* state and an isomer in *anti* state. In isomers $\mathbf{3}_{\mathbf{syn\text{-}H}}$ and $\mathbf{3}_{\mathbf{syn\text{-}Ph}}$ two indole rings and also two methyl groups are *syn* oriented around the main cavity of crown ethers. $\mathbf{3}_{\mathbf{syn\text{-}H}}$ is a *syn* isomer of benzylic C–H bond to the indole rings whereas; $\mathbf{3}_{\mathbf{syn\text{-}Ph}}$ is a *syn* isomer of phenyl ring to the indole rings. Isomer $\mathbf{3}_{\mathbf{anti}}$ is an *anti* oriented indole rings and also methyl groups which seems to be more stable than *syn*-isomers. The *HyperChem* full optimizations without any constraint were carried out for each isomer in compounds **3a**–**e**. Table 1 reports the optimized energies of the three different isomers of **3a**–**e**.

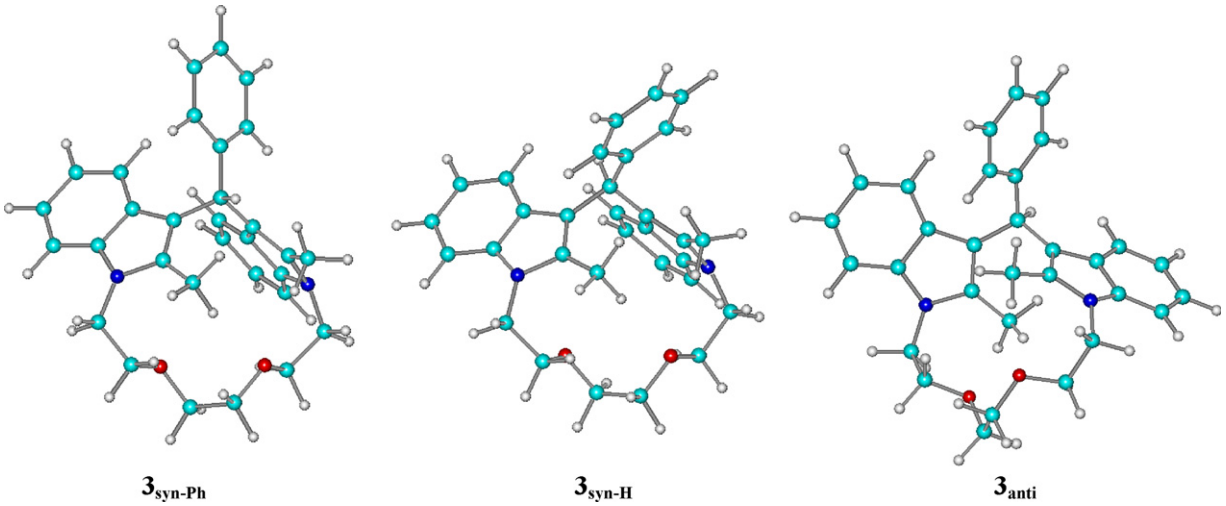

Fig. 1. Optimized structures of isomers $\mathbf{3}_{\mathbf{syn\text{-}H}}$, $\mathbf{3}_{\mathbf{syn\text{-}Ph}}$ and $\mathbf{3}_{\mathbf{anti}}$.

Table 1
Calculated energies (kcal/mol) of different isomers for compounds **3a**–**e**.

Crown	Isomer $\mathbf{3}_{\mathbf{syn\text{-}H}}$	Isomer $\mathbf{3}_{\mathbf{syn\text{-}Ph}}$	Isomer $\mathbf{3}_{\mathbf{anti}}$	ΔE_1 [a]	ΔE_2 [b]
3a	−905,504.899	−905,505.207	−905,506.534	−0.308	−1.635
3b	−929,863.384	−929,864.881	−929,865.723	−1.497	−2.339
3c	−1,192,093.417	−1,192,094.229	−1,192,109.473	−0.811	−16.056
3d	−2,511,597.467	−2,511,598.650	−2,511,614.788	−1.181	−17.321
3e	−1,032,443.252	−1,032,444.872	−1,032,445.601	−1.620	−2.349

[a] $\Delta E_1 = E\ (\mathbf{3}_{\mathbf{syn\text{-}Ph}}) - E\ (\mathbf{3}_{\mathbf{syn\text{-}H}})$.
[b] $\Delta E_2 = E\ (\mathbf{3}_{\mathbf{anti}}) - E\ (\mathbf{3}_{\mathbf{syn\text{-}H}})$.

Table 2
The detail results of each reaction including yields and percentage of isomers in compounds **3a–e**.

Entry	*p*-R-C_6H_4-CHO	Yield %	Crown	Isomer $\mathbf{3}_{\mathbf{syn\text{-}H}}$ (%)	Isomer $\mathbf{3}_{\mathbf{syn\text{-}Ph}}$ (%)	Isomer $\mathbf{3}_{\mathbf{anti}}$ (%)
1	H	70	**3a**	25	25	50
2	Me	82	**3b**	25	25	50
3	Cl	65	**3c**	22	27.5	50.5
4	Br	67	**3d**	24	24	52
5	NO_2	80	**3e**	20.5	32	47.5
6	OH	62	**3f**	22.5	25	52.5

However, this calculation suggests that whereas *syn* isomers have a small differences in calculated energies [−0.31 − (−1.62) kcal/mol] for all compounds **3a–e**, *anti* isomers are more stable than *syn* isomers especially in the cases of **3c** (16.05 kcal/mol) and **3d** (17.32 kcal/mol).

Also, these calculations are verifying that anti isomer in which two methyls are less hindered, is the most stable and therefore, in the ^{1}H NMR spectrum of **3e**, the signal at 6.17 ppm is assignment to benzyl proton of $\mathbf{3}_{\mathbf{anti}}$. Percentage of isomers can be easily obtained from relative integration of them. Similarly, percentage of each isomer in compound **3a–d** can be determined with ^{1}H NMR spectrum. Table 2 shows the detail results of each reaction including yields and isomer ratios in compounds **3a–e**. Molecular dynamic studies in low temperatures (−10 °C to −35 °C) showed that these isomers do not convert together (not shown). Accordingly, we assigned these signals to the restricted isomers.

2. Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer and only noteworthy absorptions are listed. The ^{1}H NMR (500 MHz) spectra were recorded on a Bruker DRX500 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constant *J* are given in Hz. The mass spectra were scanned on a Varian. Mat CH-7 at 70 ev. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. $Fe(HSO_4)_3$ was prepared according to the published method [17]. Other reagents which were commercially available, obtained from Merck and Aldrich companies.

2-Methyl-1-(2-2-[2-(2-methyl-1H-1-indolyl)ethoxy]ethoxyethyl)-1H-indole **2**. Indole **1** (0.5 g, 4.27 mmol) was added to a suspension of NaOH (0.256 g, 6.41 mmol) in dry DMF (30 mL), was stirred at 0 °C under nitrogen atmosphere. A dry DMF (10 mL) solution of triethylene glycol ditosylate (1.1 g, 2.14 mmol) was added dropwise to the suspension with stirring for 50 min at room temperature. After the reaction was complete, the organic solution was filtered and evaporated in vacuum, extracted with EtOAc (3× 20 mL) and washed with water and brine, then dried over anhydrous Mg_2SO_4 and recrystallized in ethanol afforded 1.42 g (85%) **2** as a light yellow crystals. M.p.: 170–172 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.40 (s, 6H), 3.39 (s, 4H), 3.63 (t, 4H, *J* = 5.9 Hz), 4.18 (t, 4H, *J* = 5.9 Hz), 6.21 (s, 2H), 6.93–7.38 (m, 6H), 7.38–7.58 (m, 2H). MS (70 eV): *m/z* 376 (M+). Anal. calcd. for $C_{24}H_{28}N_2O_2$ (376.49): C, 76.56; H, 7.50; N, 7.44. Found: C, 76.26; H, 7.41; N, 7.20.

*General procedure for the synthesis of crowns **3a–f***. Typical procedure: A mixture of bis-indole **2** (0.510 g, 1.30 mmol), benzaldehyde (1.30 mmol) and $Fe(HSO_4)_3$ (10 mol%) in dichloromethane (30 mL) was stirred at room temperature for 60 min. After complete conversion, as indicated by TLC, the reaction mixture was concentrated in vacuum, and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 3:7) to afford the pure product **3a–f**.

*2-Methyl-3-[1-[2-(2-(2-(2-methyl-1H-1-indolyl)ethoxy)ethoxy)ethyl](phenyl)methyl]-1H-indole (**3a**)*. Yellow crystals (EtOH), yield 70%, M.p.: 231–235 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.70 (s, 50% of 6H), 1.95 (s, 50% of 6H), 3.1-3.7 (m, 8H), 4.20–4.42 (m, 4H), 5.98 (s, 25% of 1H), 6.07 (s, 25% of 1H), 6.17 (s, 50% of 1H), 6.71–7.73 (m, 13H). MS (70 eV): *m/z* 464 (M+). Anal. calcd. for $C_{31}H_{32}N_2O_2$ (464.25): C, 80.14; H, 6.94; N, 6.03. Found: C, 80.05; H, 6.91; N, 5.91.

*2-Methyl-3-[1-[2-(2-(2-(2-methyl-1H-1-indolyl)ethoxy)ethoxy)ethyl](4-methylphenyl) methyl]-1H-indole (**3b**)*. Yellow crystals (EtOH), yield 82%, M.p.: 300–302 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.63 (s, 50% of 6H), 1.88 (s, 50% of 6H), 2.39 (s, 3H), 3.07–3.70 (m, 8H), 4.14–432 (m, 4H), 6.02 (s, 25% of 1H), 6.10 (s, 50% of 1H), 6.12

(s, 25% of 1H), 6.65–7.45 (m, 12H). MS (70 eV): *m/z* 478 (M+). Anal. calcd. for $C_{31}H_{32}N_2O_2$ (478.26): C, 80.30; H, 7.16; N, 5.85. Found: C, 80.05; H, 6.91; N, 6.00.

2-Methyl-3-[1-[2-(2-(2-(2-methyl-1H-1-indolyl)ethoxy)ethoxy)ethyl](4-cholorophenyl)methyl]-1H-indole ***(3c)***. Yellow crystals (EtOH), yield 65%, M.p.: 220–223 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.61 (s, 49.5% of 6H), 1.88 (s, 50.5% of 6H), 3.05–3.72 (m, 8H), 4.12–4.32 (m, 4H), 6.05 (s, 72% of 1H), 6.13 (s, 28% of 1H), 6.71–7.70 (m, 12H). MS (70 eV): *m/z* 498 (M+). Anal. calcd. for $C_{31}H_{31}ClN_2O_2$ (498.21): C, 74.61; H, 6.26; N, 5.61. Found: C, 74.30; H, 6.19; N, 5.43.

2-Methyl-3-[1-[2-(2-(2-(2-methyl-1H-1-indolyl)ethoxy)ethoxy)ethyl](4-boromophenyl)methyl]-1H-indole ***(3d)***. Yellow crystals (EtOH), yield 67%, M.p.: 270–272 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.60 (s, 48% of 6H), 1.88 (s, 52% of 6H), 3.0–3.75 (m, 8H), 4.13–4.33 (m, 4H), 6.10 (s, 76% of 1H), 6.24 (s, 24% of 1H), 6.71–7.65 (m, 12H). MS (70 eV): *m/z* 542 (M+). Anal. calcd. for $C_{31}H_{31}BrN_2O_2$ (542.16): C, 68.51; H, 5.75; N, 5.15. Found: C, 68.33; H, 5.69; N, 4.90.

2-Methyl-3-[1-[2-(2-(2-(2-methyl-1H-1-indolyl)ethoxy(ethoxy(ethyl](4-nitrophenyl)methyl]-1H-indole ***(3e)***. Yellow crystals (EtOH), yield 80%, M.p.: 259–262 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.62 (s, 52.5% of 6H), 1.91 (s, 47.5% of 6H), 3.12–3.75 (m, 8H), 4.11–4.31 (m, 4H), 5.90 (s, 20.5% of 1H), 6.00 (s, 32% of 1H), 6.20 (s, 47.5% of 1H), 6.70–7.72 (m, 10H), 8.26 (d, 2H). MS (70 eV): *m/z* 509 (M+). Anal. calcd. for $C_{31}H_{31}N_3O_4$ (509.23): C, 73.06; H, 6.13; N, 8.25. Found: C, 72.83; H, 6.01; N, 8.14.

2-Methyl-3-[1-[2-(2-(2-(2-methyl-1H-1-indolyl)ethoxy(ethoxy(ethyl](3-hidrocyphenyl)methyl]-1H-indole ***(3f)***. Yellow crystals (EtOH), yield 62%, M.p.: 258–260 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.63 (s, 47.5% of 6H), 1.88 (s, 52.5% of 6H), 3.02–3.68 (m, 8H), 4.15–4.35 (m, 4H), 4.58 (br s, 1H), 6.02 (s, 52.6% of 1H), 6.10 (s, 22.5% of 1H), 6.22 (s, 258% of 1H), 7.11–7.25 (m, 11H), 7.50–7.68 (m, 1H). MS (70 eV): *m/z* 480 (M+). Anal. calcd. for $C_{31}H_{32}N_2O_3$ (480.24): C, 77.47; H, 6.71; N, 5.83. Found: C, 77.23; H, 6.63; N, 5.62.

3. Conclusion

In conclusion, we report the synthesis of new indolyl crown ethers from reaction of bis-indolyl podand and aldehydes in the presence of $Fe(HSO_4)_3$. The reactions were carried out in a mild condition, short reaction times and high yields. Stabilities of their isomers evaluated by *HyperChem* calculations and ^{1}H NMR spectroscopy.

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