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Pyrene–azacrown ether hybrid: cation–π interaction

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Abstract—A pyrene-modified lariat ether was synthesized in order to observe the cation–π interaction in solution.

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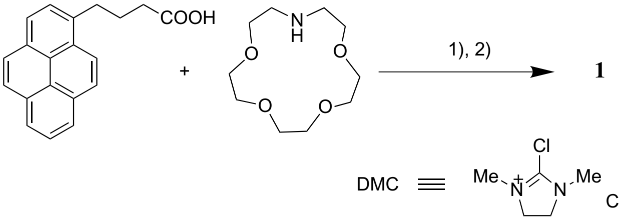
1. Introduction

The cation–π interaction has attracted more and more attention in recent chemistry because it is one of the important interactions in biological systems. For example, it is one of the origin of protein folding, a binding interaction of acetylcholine, or a key of understanding of ion channel mechanism.[1] However, in most cases in vivo or in vitro, several interactions, that is, hydrogen bond, electrostatic interaction, van der Waals interaction, etc. simultaneously operate besides the cation–π. Especially in the solution state, cations are strongly solvated and thus it is ambiguous whether the cation–π interaction operates in the polar solvents effectively. Therefore, it is important to take out the cation–π interaction as pure as possible by using a simple system in order to observe and understand the nature of the interaction. Such attempts were successfully achieved by employing the lariat-crown system.[2] Our strategy is to observe the interaction using a larger π system because more π electrons interact with cations stronger than one benzene ring. The hypothesis was supported by a recent report in which polyaromatics–Li^+ systems were investigated by theoretical calculations.[3] Furthermore, Li^+ and Na^+ interact more strongly with π electrons than other alkali metal cations.[4] For this purpose, a compound consisting of a pyrene ring and aza-15-crown-5 ether was designed.

The synthesis of compound **1** was achieved as shown in Scheme 1, and the compounds were fully characterized by the NMR, Mass, and elemental analyses.[5] Unexpectedly, the amide precursor, compound **1**, and even their cation complexes ($\mathrm{Li}^+ \subset \mathbf{1}{\cdot}\mathrm{ClO}_4^-$ and $\mathrm{Na}^+ \subset \mathbf{1}{\cdot}\mathrm{ClO}_4^-$) were not crystals but viscous oily materials.[6] Therefore, molecular structural information could not be obtained. However, the NMR spectra are powerful tools for the investigation of the interaction. In the ^{1}H NMR, the signals of the $\mathrm{CH_2{-}O{-}CH_2}$ and $\mathrm{CH_2{-}N{-}CH_2}$ protons of the azacrown ether moiety of **1** shifted to a higher field (+0.13 and +0.23 ppm, respectively) by complexation with Li^+ ($\mathrm{CDCl_3}$). In contrast to this phenomenon, the signals of the crown ether protons of the reference compound, *N*-butyl-aza-15-crown-5, shifted to a lower field (−0.1 ppm, $\mathrm{CDCl_3}$) by the complexation. In the ^{13}C NMR spectra, all signals were broadened by the complexation, and particularly, the signal of the pyrene carbon atom connected to the butyl group (C1 of pyrene ring) significantly reduced its intensity. The carbon signals of the ether moiety, O–*C*H$_2$–*N*(butyl)–*C*H$_2$–O and (crown)-N–*C*H$_2$-shifted to a higher field (+3 and ca. +3–6 ppm, respectively) by the complexation. On the



Scheme 1. Synthesis of the compound **1**: (1) 2-chloro-1,3-dimethyl-2-imidazolinium chloride, $\mathrm{CH_2Cl_2}$, $\mathrm{Et_3N}$; (2) $\mathrm{Me_2S{\cdot}BH_3}$, THF.

Keywords: Cation–π; Pyrene; Azacrown; Lariat ether.

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Table 1. Chemical shifts (^1H and ^{13}C) of crown moiety of **1** (ppm)

			$–CH_2–N–CH_2–$	$–CH_2–N=$	$–O–CH_2CH_2–O–$
CD_3CN	^1H	A	2.46 (t)	3.15 (t)	3.44–3.31
		B	2.44 (bs)	3.25	3.38, 3.35
	^{13}C	A	55.7	57.2	71.3–70.6
		B	52.0	53.4	68.9–68.3, 67.2, 67.0
$CDCl_3$	^1H	A	2.70 (t)	3.27 (t)	3.56, 3.55
		B	2.47 (t)	3.27 (t)	3.43
	^{13}C	A	54.5	56.6	70.8, 70.2, 69.9
		B	51.5–50.9 (bs)	51.5–50.9 (bs)	68.7–66.4 (bm)

A: cation-free, B: after complexation with Li^+.

bs: broad singlet, bm: broad multiplet, t: triplet. A: [**1**] = 5.0×10^{-2} mol dm^{-3}. B: [**1**] = 5.0×10^{-2} mol dm^{-3}, [$LiClO_4$] = 0.2 mol dm^{-3}.

contrary, the shifts of the aromatic protons and carbon signals were very small. Similar tendency was observed in a polar solvent, CD_3CN. The NMR data before and after complexation were summarized in Table 1. From these results, it is reasonably understood that the azacrown ether unit was significantly affected by the ring current of the pyrene ring during the complexation. Therefore, the average conformation of the complex is considered to be that shown in Figure 1.

Furthermore, the ^7Li NMR spectra were observed in order to clarify the change in the cation circumstance. The ^7Li signal of the $Li^+ \subset$ **1** appeared at −0.97 ppm (CD_3CN, aq. LiCl as an external standard), while the peak of the $Li^+ \subset$ aza-15-crown-5 appeared at −0.82 ppm. The higher field shift of the ^7Li signal ($\Delta\delta$ = +0.15 ppm) in $Li^+ \subset$ **1** apparently indicates that the Li^+ cation locates above the pyrene ring. Another evidence of the neighboring of crown moiety and pyrene ring was proved by observation of the differential NOE spectra of the $Li^+ \subset$ **1**. Irradiation of the crown –C*H*$_2$–O and O–C*H*$_2$–*N*(butyl)–C*H*$_2$–O resulted in small and medium enhancement of the proton signals of the pyrene ring, respectively. Such NOE was not observed in the case of Li^+ free ligand **1**.

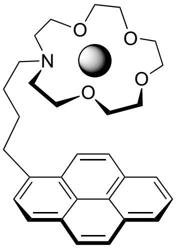

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Figure 1. Cation···π interaction of pyrene-lariat crown ether **1**.

Similar to the NMR spectral changes, the fluorescent property of **1** was changed by the complexation. In the fluorescence titration experiments, the intensity of the fluorescence of compound **1** increased as the concentration of the Li^+ or Na^+ cation increased (Fig. 2). Non-linear least-square fitting treatments of the experimental results afforded the stability constants, K_s, of $Li^+ \subset$ **1** and $Na^+ \subset$ **1** (Table 2). The stability constants, $\log K_s$, were compared to those of the related compound *N*-(4-butyl)-aza-15-crown-5 and *N*-(4-phenylbutyl)-aza-15-crown-5 (compound **3**). It is recognized from the stability constants that the large π plane (pyrene ring) enhanced the complexation ability of the azacrown ring.

Table 2. Stability constants of Li^+ and Na^+ complexes of **1** (CH_3CN), compound **3** (CD_3CN), and *N*-(4-butyl)-aza-15-crown-5 (CD_3CN) error: <±5%

	$\log K_s$ (Li^+)	$\log K_s$ (Na^+)
Compound **1**	5.4	5.3
Compound **3**	3.2[a]	2.6[a]
N-Butyl-aza-15-C-5	3.1[a]	3.6[a]

[a] NMR titration in CD_3CN.

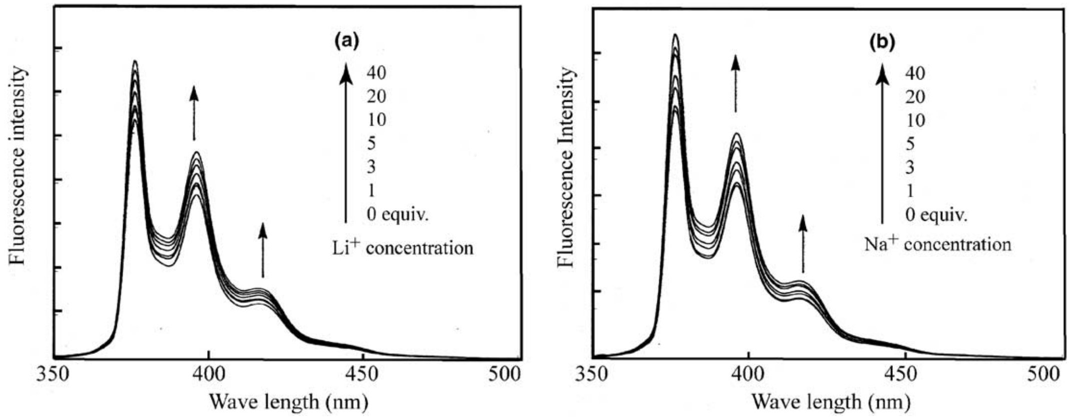
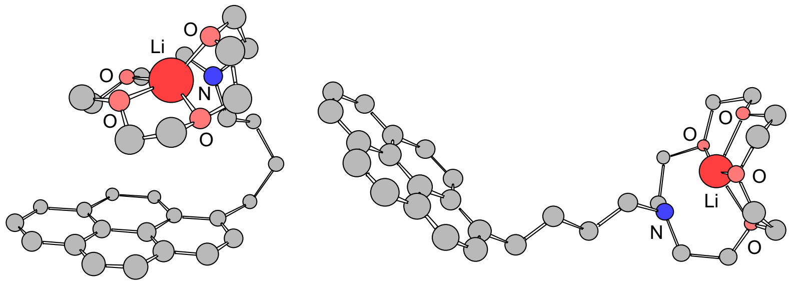


Figure 2. Fluorescence titrations of **1** with (a) $LiClO_4$, (b) $NaClO_4$ in CH_3CN at 25 °C. Concentration of **1** = 1×10^{-6} mol dm^{-3}. Excitation wavelength: 340 nm.



Conformer A Conformer B

Figure 3. Optimized structure of Li$^+ \subset$ **1** (conformers A and B) calculated by using ab initio calculations.

In the literature, strong Li$^+$ and Na$^+$ affinity of *N*-benzyl-aza-15-crown-5 (log *K* (Li$^+$) = 4.63 and log *K* (Na$^+$) = 5.88 in CH_3CN) was reported.[7] In this case, π donor closely faced to crown moiety, thus, cation–π interaction effectively assisted the complexation of the cations. This was confirmed to compare the affinity toward the cations with compound **3**, *N*-(4-phenylbutyl)-aza-15-crown-5.[8] As a result, the compound **3** showed comparable affinity with π donor-free *N*-(4-butyl)-aza-15-crown-5. Therefore, the strong complexation ability of *N*-benzyl-aza-15-crown-5 originated from the entropy effect. These results obtained above should be unequivocally attributed to the presence of effective cation–π interaction by a large π system of **1**. Furthermore, it is worth noting that the binding of Li$^+$ is slightly stronger than that of Na$^+$. Generally, aza-15-crown-5 derivatives bind Na$^+$ stronger than Li$^+$ because of the cavity size.[9] Thus, the phenomenon coincides with the fact that Li$^+ \cdots \pi$ interaction is stronger than Na$^+ \cdots \pi$ interaction.[1]

The stabilization energies of the Li$^+$ complexes were calculated by using ab initio calculations with the 6–31G basis set on possible conformers which were pre-optimized by PM3 calculations. As a result, conformer A is slightly stable (0.70 kcal mol^{-1}) than conformer B (Fig. 3). The calculation does not accurately reflect the actual experimental conditions, but it supports the experimental results and our prediction (cation–π interaction).

2. Conclusion

The combination of a pyrene ring and azacrown ether generated a new kind of host molecule. Its binding ability originated from the cation-dipole interaction (crown moiety) and the cation–π interaction (pyrene ring). Unfortunately, the molecular structures of the cation complexes of the host could not be clarified, but the NMR and the fluorescent spectra strongly indicated the effect of the cation–π interaction.

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5. Compound **2**: To a solution of aza-15-crown-5 (465 mg, 2.1 mmol), 1-pyrenebutyric acid (620 mg, 2.1 mmol), and triethylamine (490 mg, 4.8 mmol) in 30 mL of CH_2Cl_2 was added a solution of 2-chloro-1,3-dimethyl-2-imidazolinium chloride (390 mg, 2.3 mmol) in 20 mL of CH_2Cl_2 at 0 °C over a period of 10 min. The mixture was stirred for 5 h at room temperature, and then quenched with 5 mL of water. The resultant mixture was washed with water, and the organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the resultant oily material was chromatographed on silica-gel with CH_2Cl_2–acetone (90/10, v/v) as the eluent. Pale yellow oil (873 mg, 84.1%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33–7.82 (m, 9H), 3.65–3.35 (m, 20H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.20 (quint., 2H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6 (CO), 136.0, 131.1, 130.7, 129.6, 128.6, 127.2–127.0, 126.4–126.3, 125.6, 124.8–124.5, 123.3–123.3, 71.3–69.4, 50.23, 49.3, 32.7, 32.3, 27.0. HRMS (FAB): Calcd for $C_{30}H_{36}NO_5$ = 490.2593. Found 490.2593. Anal. Calcd for $C_{30}H_{37}NO_4 \cdot 1/4PhCH_3$: C, 74.39; H, 7.27; N, 2.73. Found: C, 74.10; H, 7.22; N. 2.74.
   Compound **1**: To a solution of compound **2** (378 mg, 0.77 mmol) in 20 mL of dry THF was added the borane-dimethyl sulfide complex (0.30 mL, 3.1 mmol) under an N_2 atmosphere. The mixture was heated at 50 °C overnight, and then quenched with 10 mL of water. The mixture was extracted with CH_2Cl_2 and the extracts were dried over $MgSO_4$. Removal of the solvents afforded a yellow oil, which was chromatographed on silica-gel with CH_2Cl_2–MeOH (90/10, v/v) as the eluent. Pale yellow oil (294 mg, 80.0%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, *J* = 9.5 Hz, 1H), 8.11 (t, *J* = 5.0 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.92–8.00 (m, 3H), 7.81 (d, *J* = 8.0 Hz, 1H), 3.56–3.62 (m, 16H), 3.30 (t, *J* = 8.0 Hz, 2H), 2.77 (t, *J* = 5.5 Hz, 4H), 2.60 (t, *J* = 7.0 Hz, 2H), 1.79 (m, 2H), 1.65 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.7, 131.1, 130.6, 129.4, 128.3, 127.2, 126.9, 126.8, 126.2, 125.5, 124.8, 124.5, 124.3, 123.2, 70.8, 70.2, 70.0, 56.6, 54.5, 33.4, 29.5, 27.5. FABMS: *m*/*z*: 476 ([M+H]$^+$, 100%); Anal. Calcd for $C_{30}H_{37}NO_4 \cdot$

1/3H_2O·1/3CH_2C1_2: C, 71.45; H, 7.58; N, 2.75. Found: C, 71.53; H, 7.56; N. 2.65. HRMS (FAB) Calcd for $C_{30}H_{38}NO_4$ ($M{+}H^+$) = 476.2801. Found 476.2800.

6. $Li^+ \subset \mathbf{1}\cdot BF_4{}^-$: ^{1}H NMR ($CD_3$ CN, 400 MHz): δ 8.26–7.81 (m, 9H), 3.38–3.35 (m, 16H), 3.28–3.22 (m, 4H), 2.44 (bs, 4H), 1.68 (quint, 2H), 1.43 (bs, 2H). ^{13}C NMR (CD_3 CN, 100 MHz): δ 137.8, 132.1, 131.7, 130.5, 129.3, 128.3, 128.2, 127.9, 127.3, 126.9, 125.7, 125.7, 125.6, 125.5, 125.4, 124.4, 68.9, 68.5, 68.3, 67.2, 67.0, 53.4, 52.0, 33.6, 30.3, 24.4. FABMS: *m*/*z*: 476.3, 482.3 ($[M]^+$, 75%; $[M{+}Li]^+$, 85%).

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8. *N*-(4-Phenylbutyl)-aza-15-crown-5**3**: A solution of 4-phenyl-1-bromobutane (630 mg, 2.96 mmol), monoaza-15-crown-5 (610 mg, 2.78 mmol), and Cs_2CO_3 (1.32 g, 4.05 mmol) in 10 mL of CH_3CN was heated at 80 °C for 20 h. The mixture was evaporated and 20 mL of water was added. The mixture was extracted with CH_2Cl_2 and the extracts were evaporated. The resultant oily product was column chromatographed on Chromatorex-NH (Fuji Silysia) with CH_2Cl_2 as an eluent. Colorless oil (0.950 mg, 91.4%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13–7.14 (m, 5H), 3.63–3.58 (m, 16H), 2.71 (t, $J = 6.1$ Hz, 4H), 2.59 (t, $J = 7.5$ Hz, 2H), 2.50 (t, $J = 7.2$ Hz, 2H), 1.65–1.48 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.0, 128.1, 128.0, 127.7, 127.6, 127.5, 125.4, 124.9, 70.6, 70.0, 69.7, 68.6, 56.4, 54.3, 35.5, 29.0, 26.7. Anal. Calcd for $C_{20}H_{33}NO_4$·1/6CH_2C1_2: C, 66.25; H, 9.19; N, 3.83. Found: C, 66.24; H, 9.22; N. 3.87. HRMS (EI) Calcd for $C_{20}H_{33}NO_4$ (M^+) = 351.2409. Found 351.2382.

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