Formation of pseudo[3]rotaxanes containing calix-bis-crowns and secondary ammonium ions and their thermodynamic stabilities in a solution: preorganization by second macrocycle and nonallosteric behavior exhibited by large crown cavities

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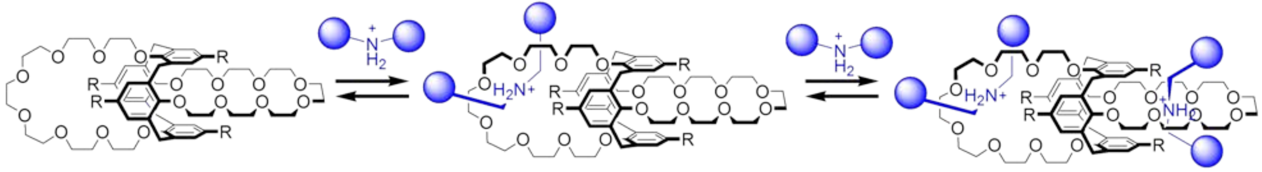

Formation of pseudo[3]rotaxanes containing calix-bis-crowns and secondary ammonium ions and their thermodynamic stabilities in a solution: preorganization by second macrocycle and nonallosteric behavior exhibited by large crown cavities

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Abstract

This paper describes the formation of pseudo[3]rotaxanes containing calix[4]-bis-crowns, exhibiting a 1,3-alternate conformation and large crown cavities, and secondary ammonium ions. The first and second association constants of pseudo[3]rotaxane formation are moderate (K_1 = 175, K_2 = 100 M^{-1}) and are higher than that of the corresponding pseudo[2]rotaxane (K = 24 M^{-1}), consisting of a calix[4]-mono-crown and the same secondary ammonium ion.

Keyword: Rotaxane; calixarene; crown ether; thermodynamic stability; hydrogen bond

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Calixcrowns,[1] combining calixarene and crown ether moieties, are an attractive family of macrocycles because they have different cavity shapes on the basis of the conformation of calixarenes, as well as cavity features from the calixarene and crown ether. Among them, fascination for calix[4]-bis-crowns with a 1,3-alternate conformation stems from the following properties: (1) two crown cavities can form a dinuclear complex, (2) two crowns can separately exist in a contrary direction through the calixarene core and (3) unsymmetrical calix-bis-crowns can be synthesized.[2] For example, calix[4]arene-bis-(crown-6), one of the well-known calixcrowns, are selectively used for cesium ion recognition, and its application have been deeply studied, including solvent extraction[3] or liquid membrane transport,[4] solution thermodynamics,[5] detection,[6] X-ray crystal structure and molecular modelling[7] Recently, a calix-bis-crown with hard and soft crown cavities for K^+ and Ag^+ was synthesized using an asymmetrical bis-crown.[8]

However, these studies mainly focused on the affinities between cations and calix-bis-crowns with small cavity sizes (up to crown-7); therefore, the crown ether moieties could only act as hosts for metals or primary ammonium ions. Herein, we report the synthesis of new calix[4]-bis-(crown-8) with a large cavity size and the formation of pseudo[2]- and [3]rotaxanes consisting of the calix[4]crown and secondary ammonium ions,[9] and their thermodynamic parameters by NMR spectroscopy. Moreover, we synthesized a tetrabrominated calix[4]-bis-(crown-8) and investigated the neighbouring effects of bromine atoms on association (thermodynamic stability) with ammonium ions. The calix[4]-bis-crown can be functionalized with dumbbell-like secondary ammonium ion(s) through the formation of pseudorotaxanes, which is different from calix[4]crown–metal complexation, because this method, in particular, can externally attach various functionalities to the calix[4]-bis-crown.

The calix[4]-bis-crown was synthesized by a two-step cyclization procedure, as reported for synthesis of unsymmetrical calix-bis-crowns (Scheme 1).[8] The first cyclization of calix[4]arene **1**[10] with hepta(ethylene glycol) ditosylate provided the calix-mono-(crown-8) (**2a**) in 47% yield. Deprotection of benzyl groups followed by second cyclization of **2b** with the same ditosylate afforded the desired calix[4]-bis-crown-8 (**3a**). The ^{1}H NMR spectrum of **3a** indicated the calix[4]-bis-crown with a 1,3-alternate conformation; only two aromatic signals (H_J and H_K) and a singlet assigned to the methylene protons (H_H) of calixarene were observed in the spectrum (Figure 2a). Finally, treatment of **3a** with excess bromine provided the corresponding tetrabrominated calix[4]-bis-crown (**3b**). In addition, we tried to directly synthesize the calix[4]-bis-(crown-8) (**3a**). Double cyclization of unprotected calix[4]arene with two equivalents of the ditosylate afforded **3a** in 18% yield after purification by size exclusion chromatography.

The formation of pseudo[2]rotaxanes and pseudo[3]rotaxanes using **2a**, **3a** and **3b** as macrocycles and **4** as a dumbbell-shaped molecule was monitored by ^{1}H NMR spectroscopy. We reported the regulation of the association and dissociation rates of [22–30]crown ethers and dumbbell-like secondary ammonium salts by varying the stopper groups of the dumbbells.[11,12] We chose the 3,5-dimethylbenzyl group as a suitable stopper to obtain the association constants of pseudorotaxanes using single-point determination on the basis of previous results and molecular modelling of calix[4]-bis-crown (**3a**).

For example, the ^{1}H NMR (3:2 $CDCl_3$–CD_3CN) spectrum of a mixture of mono-crown **2a** (100 mM) and secondary ammonium salt **4** (100 mM) reveals the formation of the pseudo[2]rotaxane (**2a-4**): downfield-shifted signals for the benzylic protons of the ammonium ion (H_2 at 4.22 ppm) and upfield-shifted signals for aliphatic protons of the crown ether moiety (e.g., H_a at 2.98 ppm, H_b at 3.22 ppm and H_f at 3.19 ppm) were observed in the spectrum (Figure 1c). These observations are characteristics of crown ether/dibenzylammonium-type pseudorotaxanes.[9] Similarly, ^{1}H NMR (3:2 $CDCl_3$–CD_3CN) titration of bis-crown **3a** and ammonium salt **4** was performed; the spectrum resulting from a 1:2 mixture of **3a** and **4** is shown in Figure 2b. Two new sets of signals, based on pseudo[2]- and [3]rotaxanes (**3a-4** and **3a-4$_2$**) (Scheme 2), exhibited increased intensity concomitant with the increase in the amount of ammonium salt. Finally, a set of signals were mainly observed in the ^{1}H NMR spectrum of a 1:10 mixture of **3a** and **4** (Figure 2c); the chemical shifts of benzylic proton signals of dumbbell parts ($H_{2'}$ at 4.08–4.18 ppm) and aliphatic proton signals of calix-bis-crown (e.g., $H_{a'}$ at 2.98 ppm, $H_{b'}$ at 3.22 ppm and $H_{f'}$ at 2.98 ppm) supported the formation of the corresponding pseudo[3]rotaxane (**3a-4$_2$**). A correlation existed between the signals of the crown ether unit's protons ($H_{a'-c'}$) and protons ($H_{3'}$) of the ammonium component in the NOESY spectra of the 1:1 mixture of mono-crown **2a** and **4** (SI Figure S3b) and 1:10 mixture of **3a** and **4** (SI Figure S5b). Similarly, we performed NMR experiments using bromo-bis-crowns **3b** and ammonium salt **4** to reveal the formation of pseudo[2]- and [3]rotaxanes (**3b-4** and **3b-4$_2$**) (SI Figure S1, 7-9).

The association constant of the pseudo[2]rotaxane (**2a-4**) was determined to be 23.6 (±2.3) M^{-1} at 20 °C on the basis of the integration of H_n proton signals (Figure 1c).[13] The association constants for **3a-4** and **3a-4$_2$** (using the integrations of H_k proton signals in Figure 2) and for **3b-4** and **3b-4$_2$** (using H_j proton signals in Figure 3) were obtained (Table 1) in the same way. These association constants, K_1 and K_2, of bis-crowns (**3a** and **3b**) are close to those of typical 27- and 30-membered circular crown ethers[11] but larger than that of mono-crown **2a**. This difference in association constants is probably because of favourable preorganization of the rigid structure of bis-crowns (**3a** and **3b**). The bromine atoms could not effectively function as hydrogen bond donors for the benzylic protons of the ammonium ion at ambient temperature. Interestingly, the K_1 and K_2 values of the bis-crowns are similar; there is no large negative allosteric effect in the formation of pseudo[3]rotaxanes. Kríz *et al.* reported an interaction of cesium ions with calix[4]arene-bis(benzo-18-crown-6) and a large negative allosteric effect in the formation of the second complex (log K_1 = 8.8 and log K_2 = 6.3) because of the strong electrostatic repulsion of the two cesium ions.[14] In addition, Katsu *et al.* reported that only one crown moiety of calix[4]-bis-(crown-6) could trap a methylammonium ion.[2b] Why is there no negative allosteric effect in bis-crowns (**3a** and **3b**) and ammonium ions (**4**)? A significant electrostatic repulsion might not be produced owing to the long distance between two ammonium ions in pseudo[3]rotaxanes (**3a-4$_2$** and **3b-4$_2$**), as both crowns (**3a** and **3b**) have large cavities. For the pseudorotaxane formation, the ammonium ions cannot sink into the calixarene cavity because of bulky functionalities around the ammonium moiety. Furthermore, a π-cation interaction between the calixarene core and cesium cation should exist, which promotes cesium cation binding.

Next, we performed variable temperature NMR experiments (0–40 °C) using mixtures of crowns (**2a**, **3a** and **3b**) and ammonium salt **4**, respectively. The plots of ΔG versus temperature for the equilibria (formation of pseudo[2]- and [3]rotaxanes) yielded straight lines (SI Figure S10), we utilized these plots to determine the enthalpic (ΔH) and entropic (ΔS) parameters, respectively (Table 1). The large enthalpy and entropy values of **2a** compared with those of pseudorotaxanes from bis-crowns (**3a** and **3b**) must be attributed to the flexibility of pseudo[2]rotaxane **2a-4**. The structure of bis-crowns should be suitable for ammonium binding because of the construction of the second macrocycles, which afford favourable crown shapes for hydrogen bonding, providing small enthalpy and entropy values for bis-crowns **3** (more enthalpically favourable). Comparing the enthalpy values (both ΔH_1 and ΔH_2) of bis-crowns **3a** and **3b**, smaller values of **3b** could result from expected N^+CH–Br hydrogen bonds between bromine atoms and benzylic protons of the ammonium ion. The hydrogen bonds and bulky bromine atoms might incur an entropic cost owing to the loss of freedom of ammonium ions in pseudorotaxanes (**3b-4** and **3b-4$_2$**); the association constants of bis-crowns (**3a** and **3b**) are comparable at ambient temperature.

Recently, the Lee group expanded calix[4]-bis-crown chemistry into metal–organic frameworks on the basis of exocoordinated 3D networks through coordination bonds.[15] Our studies could construct alternative higher-order networks of calix[4]-bis-crowns because the formation of pseudorotaxanes can provide desirable functionalities on the outside of calix[4]-bis-crowns; the construction of higher levels of molecular architecture could be enabled by suitable functionalities on dumbbell-like ammonium salts, because the first and second association constants for the formation of pseudo[3]rotaxanes are moderate and similar.

In conclusion, this effort has led to the construction of novel pseudorotaxanes containing secondary ammonium ion(s) and calix-crowns with a 1,3-alternate conformation possessing hepta(ethylene glycol) unit(s). The NMR titration experiments revealed that bis-crowns have suitable cavity shapes for ammonium ions compared with those of mono-crowns, and that the difference in association constants originated by enthalpically driven forces. Furthermore, unusual nonallosteric effects on second association between bis-crowns and ammonium ions were observed.

Acknowledgements

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Supplementary data

Supplementary data (NMR titration of calix[4]-bis-(crown-8) **3b** and ammonium salt **4**, 2D NMR spectra of **2a**, **3a**, and **3b** in the absence, and in the presence of **4**, Arrhenius plots for the formation of the pseudo[2]- and [3]rotaxanes, experimental data of **2a**, **3a**, and **3b**) associated with this article can be found, in the online version.

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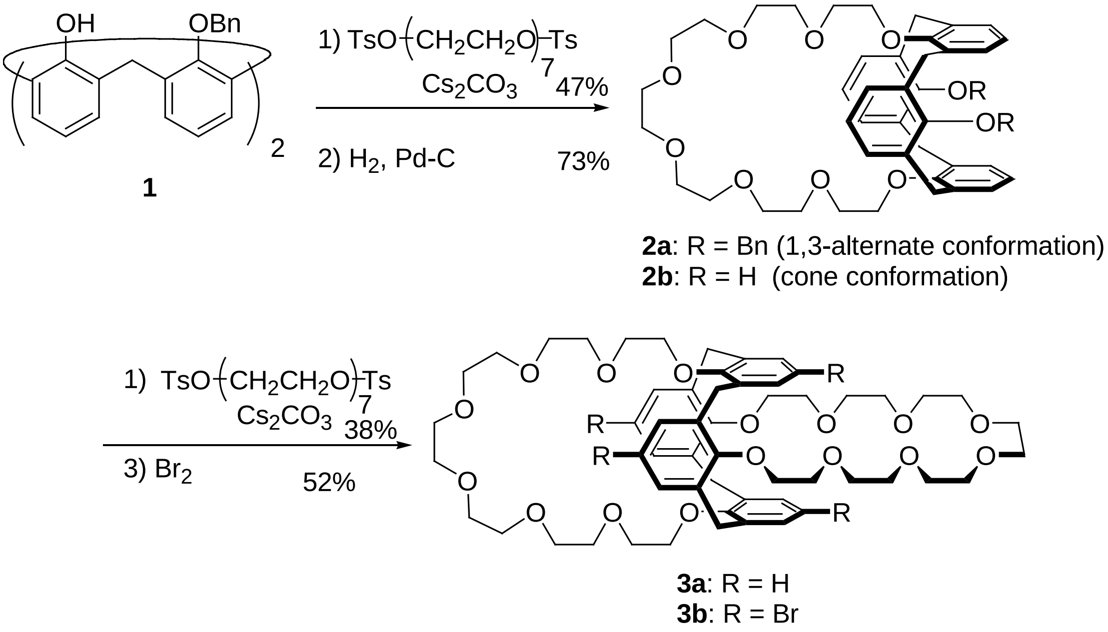

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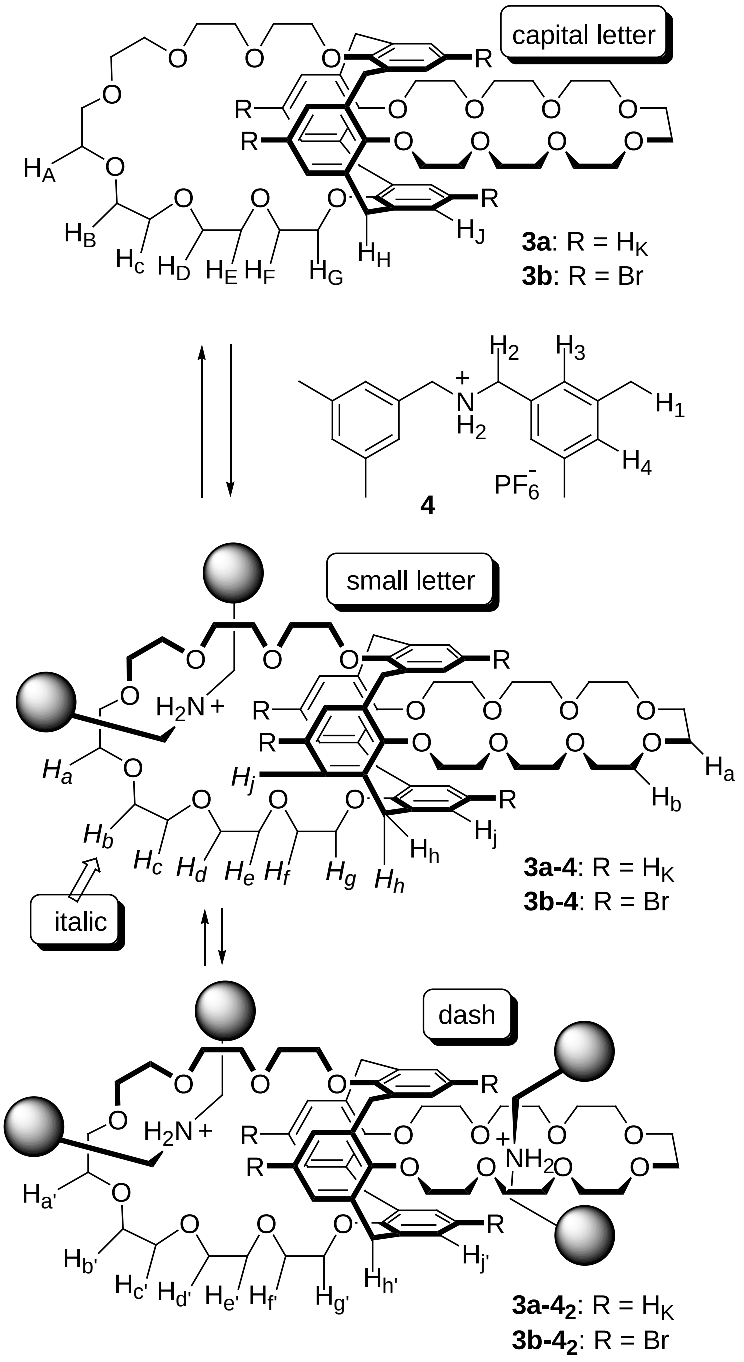
2a: R = Bn (1,3-alternate conformation)
2b: R = H (cone conformation)

3a: R = H
3b: R = Br

Scheme 1. Synthesis of calix-mono-(crown-8) (**2a**) and calix[4]-bis-(crown-8) derivatives (**3a** and **3b**).



Scheme 2. Formation of pseudo[2]- and pseudo[3]rotaxanes.

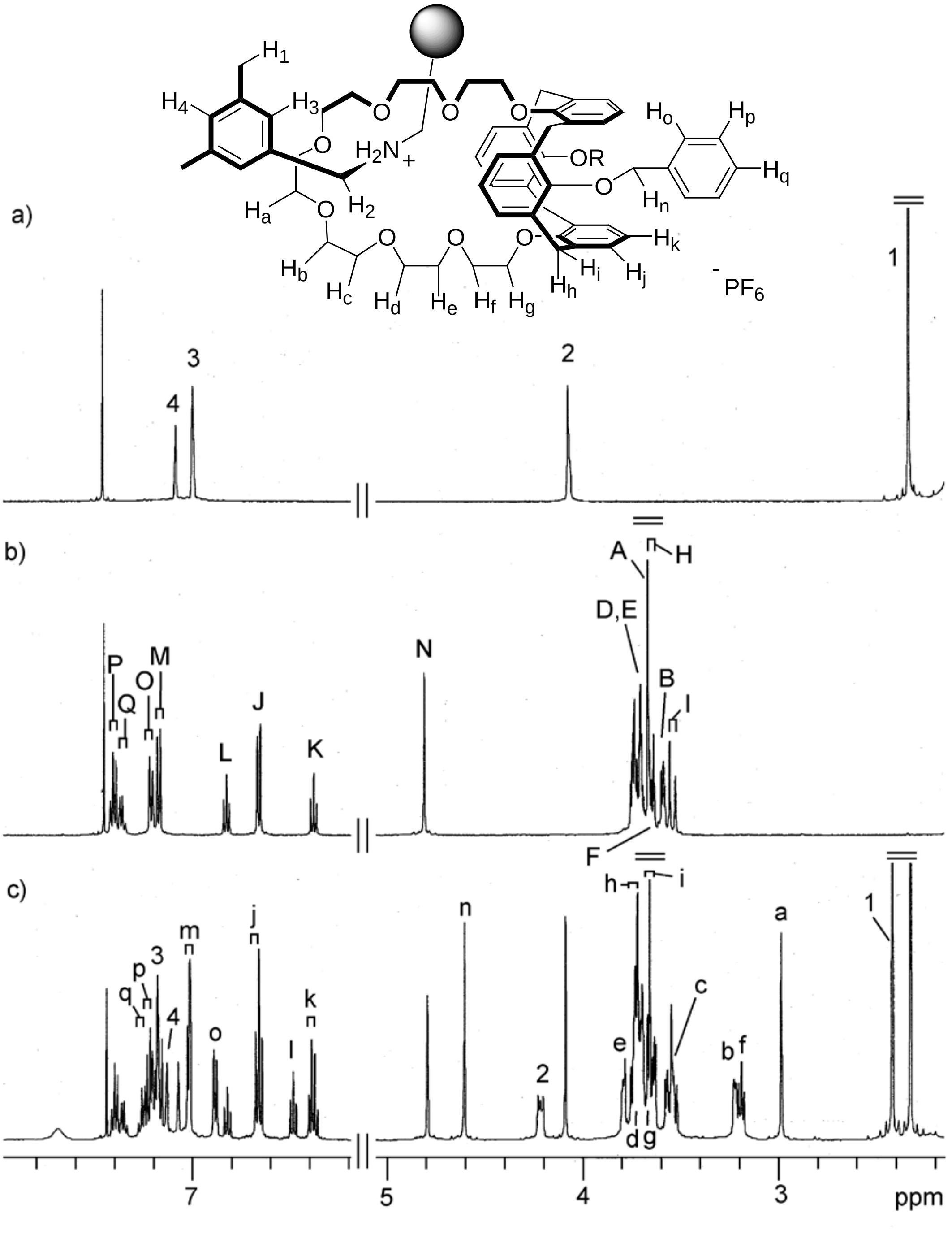


Figure 1. ^{1}H NMR (500 MHz, CDCl$_3$–CD$_3$CN (3:2), 30 °C) spectra. (a) Ammonium salt **4**, (b) calix[4]-mono-crown **2a** and (c) a mixture of **2a** (100 mM) and **4** (100 mM). Upper-case letter: uncomplexed **2a**, and lower-case letter: complexed **2a** (pseudorotaxane **2a**-**4**).

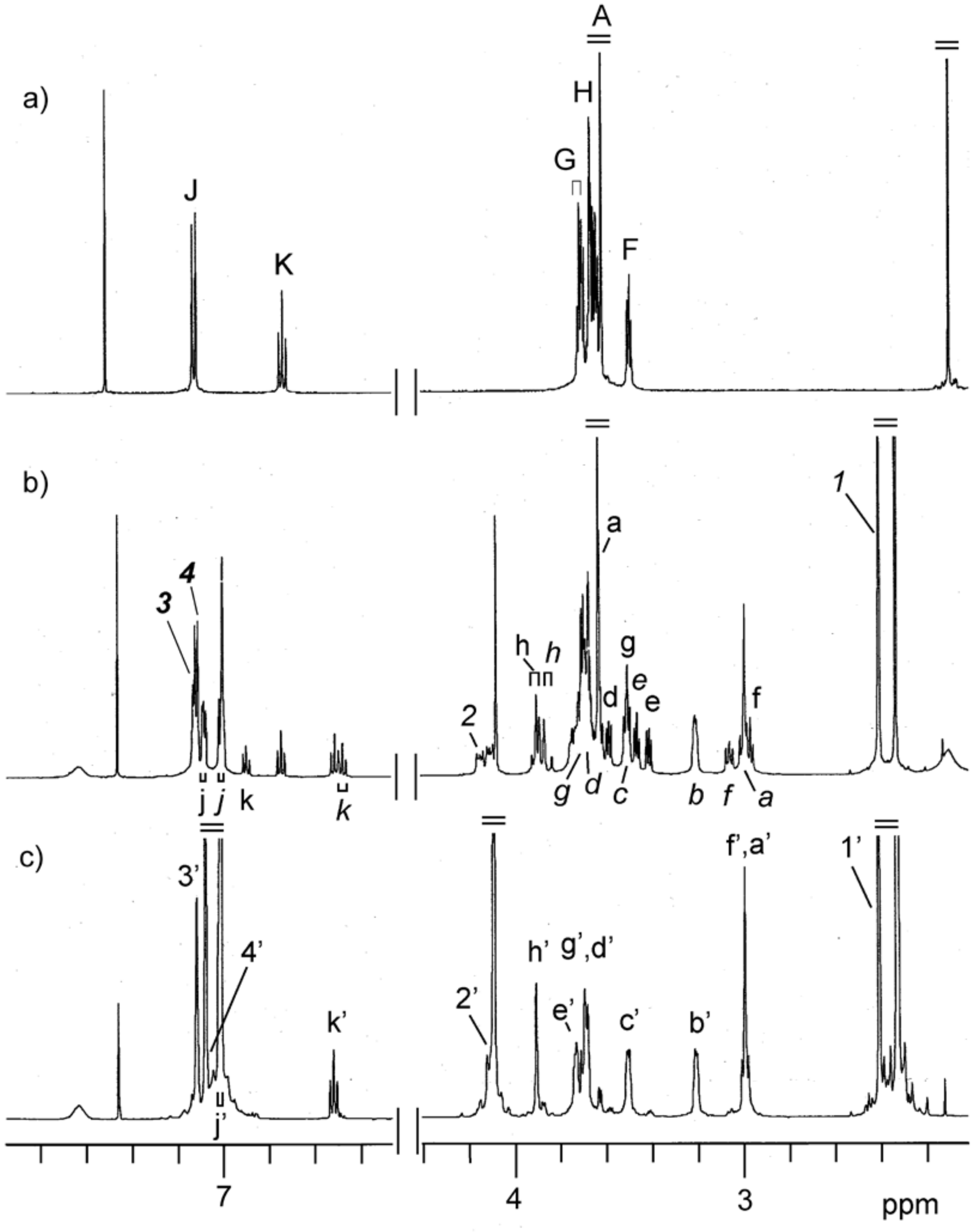


Figure 2. ^{1}H NMR (500 MHz, $CDCl_3$–CD_3CN (3:2), 30 °C) spectra. (a) Calix[4]-bis-crown **3a**, (b) a mixture of **3a** (10 mM) and **4** (20 mM), and (c) a mixture of **3a** (10 mM) and **4** (100 mM). Upper-case letter: uncomplexed **3a**, lower-case letter: uncomplexed site of pseudo[2]rotaxane **3a-4**, italic: complexed site of pseudo[2]rotaxane **3a-4** and dash: pseudo[3]rotaxane **3a-4$_2$**. For atom labels, see Scheme 2.

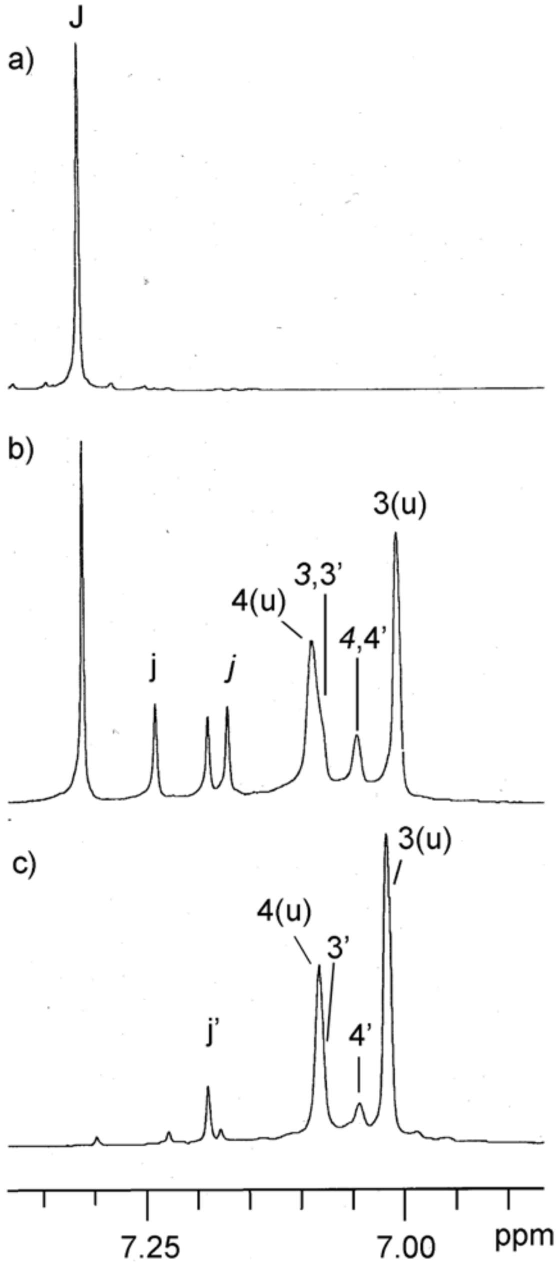


Figure 3. Partial ^{1}H NMR (500 MHz, $CDCl_3$–CD_3CN (3:2), 30 °C) spectra. (a) Calix[4]-bis-crown **3b**, (b) a mixture of **3b** (10 mM) and **4** (20 mM) and (c) a mixture of **3b** (10 mM) and **4** (100 mM). Upper-case letter: uncomplexed **3b**, lower-case letter: uncomplexed site of pseudo[2]rotaxane **3b-4**, italic: complexed site of pseudo[2]rotaxane **3b-4**, dash: pseudo[3]rotaxane **3b-4$_2$** and (u): uncomplexed **4**. For atom labels see Scheme 2.

Table 1. Thermodynamic parameters of formation of pseudo[2]rotaxanes **2a-4**, **3a-4** and **3b-4**, and pseudo[3]rotaxanes **3a-4$_2$** and **3b-4$_2$**.

	association constants (M^{-1}) at 20 °C	ΔH (kJ/mol)	ΔS (J/K•mol)
mono-crown **2a**	23.6 ± 2.3	-17.5 ± 1.7	-35.3 ± 6.9
bis-crown **3a**	K_1 = 175 ± 40 K_2 = 100 ± 24	ΔH_1 = -29.1 ± 1.5 ΔH_2 = -22.5 ± 2.4	ΔS_1 = -60.6 ± 5.9 ΔS_2 = -42.6 ± 7.0
Br-bis-crown **3b**	K_1 = 136 ± 26 K_2 = 95.3 ± 32	ΔH_1 = -35.4 ± 3.1 ΔH_2 = -36.6 ± 4.5	ΔS_1 = -84.2 ± 5.8 ΔS_2 = -89.6 ± 16