

Synthetic Receptors for Neutral Molecules: Complexation of $\text{H}_3\text{O}^+(\text{H}_2\text{O})_n$ ($n = 0-2$) by 2-Sulfo-1,3-xylyl Crown Ethers

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Abstract: Macrocycles with an intraannular sulfonyl group, viz. 2-sulfo-1,3-xylyl-3*n*-crown-(*n* - 1), (*n* = 5-11, **6a-g**), were synthesized by reaction of 2-(bromomagnesio)-1,3-xylyl crown ethers **4**, generated in situ from 2-bromo-1,3-xylyl crown ethers **1** and *n*-butyllithium followed by transmetalation with MgBr_2 and with sulfur chloride and subsequent hydrolysis of the chlorosulfonyl group in **5**. The structures of five macrocycles [**5a**, **6b**·Li·H₂O, **6a**·H₂O, **6c**·(H₂O)₂, and **6e**·(H₂O)₃] were determined by X-ray crystallography. In the complexes of the sulfonic acids and water, the proton of the acidic group is transferred to a water molecule (or to a cluster of two or three water molecules, respectively). The hydronium ion, thus formed, is present in a perching complex with **6a** and encapsulated in both other complexes [**6c**·(H₂O)₂ and **6e**·(H₂O)₃]; it clearly has a *pyramidal* geometry. The $\text{p}K_a$ values of the crown ethers **6** in water gradually decrease with increasing ring size from 2.5 (**6a**) to 2.0 (**6g**). This indicates that the sulfonic acid group in the macrocyclic cavity is a much weaker acid than benzenesulfonic acid ($\text{p}K_a$ -2.8). The low "bulk" acidity can be explained by complexation of H_3O^+ in the macrocyclic cavity, as a special case of a low K_d of the tight ion pair formed by ionization of the acidic group.

Although, starting with the pioneering work by Pedersen,¹ most of the complexation studies with crown ethers have concentrated on metal cations² or organic cations³ as the guest species, there is an increasing interest in the complexation of *neutral* molecules.⁴ After we had proven that simple crown ethers form complexes with neutral guests like nitromethane,^{4b} malononitrile,^{4c,d} and urea^{4e} in apolar solvents, we studied several ways to enhance the stability of such complexes.

Urea has been successfully complexed in ternary complexes of metallomacrocycles in which an electrophilic cation, e.g., Li^+ or UO_2^{2+} , provides an additional binding site for the neutral guest.⁵ As an alternative we have shown that intraannular acidic groups, like NH^+ , OH , or COOH , may participate in the complexation of urea via hydrogen bonding with urea.⁶ A similar approach was recently successfully applied for the complexation of urea by Bell,⁷ and of barbiturates by Hamilton et al.⁸ Rebek et al. have demonstrated that this methodology can be used for the complexation of a variety of neutral guests by receptor molecules that have acidic groups properly arranged in molecular clefts.⁹ In all these complexes hydrogen bonding is important, but in none of these cases is the proton actually transferred from host to guest. We felt that such a proton transfer might increase the stability of complexes between neutral hosts and guests.

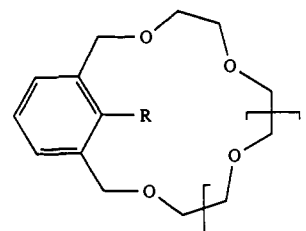
Consequently, we have investigated systematically the acidity of intraannular acidic groups as a function of the size and shape of the macrocyclic cavity.^{6,10} We found interesting correlations between acidity and ring size of crown ethers that have intraannular pyridinium or carboxyl substituents. In a number of cases we could show that specific solvation of the acidic group by complexed water molecules may lower the acidity of such macrocycles by 0.6-1.0 $\text{p}K_a$ unit. However, a proton transfer between the host and the solvent molecule, or a complexed urea molecule, has not been observed in the X-ray structures of the crystalline complexes.^{6a,10}

In this paper we report the first example of *proton transfer from an intraannular acidic group of a crown ether to a water molecule that is complexed in the molecular cavity*. Our result may have consequences for the reported highly perturbed $\text{p}K_a$'s of acidic groups in proteins that are generally attributed to the polarity of the microenvironment of the acidic group in the enzymes.¹¹

Results and Discussion

Previously we have shown that in the presence of strong acids, e.g., nitric, picric, or *p*-toluenesulfonic acid, urea is complexed

Chart I



1 a-g	<i>n</i> = 1-7	R = Br
2 a-g	<i>n</i> = 1-7	R = SO ₂ H
5 a	<i>n</i> = 1	R = SO ₂ Cl
6 a-g	<i>n</i> = 1-7	R = SO ₂ H
7 e	<i>n</i> = 5	R = SO ₂ NH-t-Pr

by 18-crown-6 in the form of the corresponding uronium salts.¹² Because, of these three acids, only the *p*-toluenesulfonic acid

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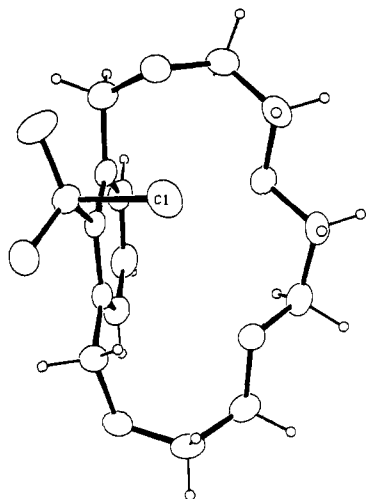
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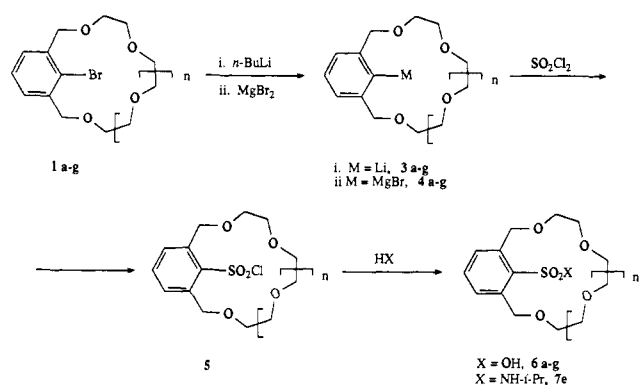
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Figure 1. Crystal structure of **5a**.

Scheme 1



residue is suitable for incorporation in a macrocyclic cavity, we have investigated the synthesis of 2-sulfo-1,3-xylyl crown ethers **6** (Chart I). In principle such compounds can be obtained by oxidation of the corresponding sulfinic acids by potassium permanganate or hydrogen peroxide.¹³ The 2-sulfinio-1,3-xylyl crown ethers **2** were synthesized by the general method that we have recently developed for the 2-substituted 1,3-xylyl crown ethers starting from 2-bromo-1,3-xylyl crown ethers **1**.¹⁴ Halogen to lithium exchange by reaction with *n*-butyllithium at -70°C followed by reaction with SO_2 converts **1** into 2-sulfinio-1,3-xylyl crown ethers in satisfactory yields. However, oxidation of the crown ethers **2** gave rise to mixtures of products, probably due to disproportionation of the sulfinic acids. As an alternative we have reacted the 2-lithio- or 2-(bromomagnesio)-1,3-xylyl crown ethers (**3** and **4**, respectively) with sulfonyl chloride.¹⁵ In order to compare the reactivity of the 2-lithio and the 2-bromomagnesio derivatives,¹⁶ we have reacted both 1,3-xylyl-27-crown-8 derivatives (**3e** and **4e**, respectively) with SO_2Cl_2 . The subsequent reaction with isopropylamine was used to convert the reactive 2-(chlorosulfonyl)-1,3-xylyl crown ether into the stable 2-[(*N*-isopropylamino)sulfonyl]-1,3-xylyl-27-crown-8 (**7e**). The crude product from the reaction of **3e** contained less than 10% **7e**, but from the reaction of **4e** we isolated **7e** in 48% yield. Based on these results, the synthesis of 2-sulfo-1,3-xylyl-3*n*-crown-(*n* - 1) ethers **6** was

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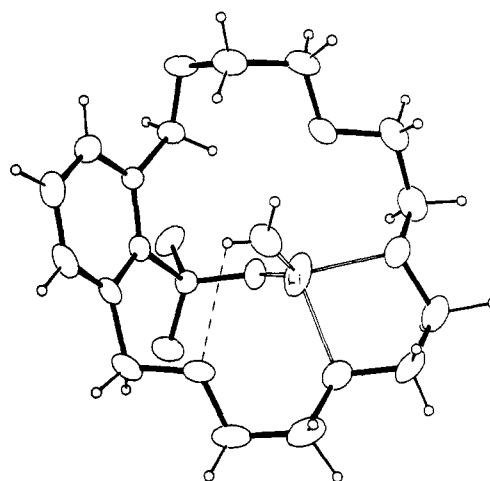
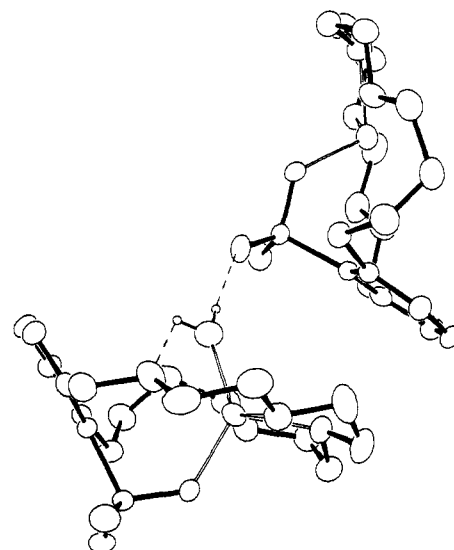
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Figure 2. Crystal structure of **6b**·Li·H₂O. Hydrogen bonds indicated by dashed lines and Li⁺ coordination by open bonds.Figure 3. Crystal structure view of the coordination of a water molecule by two **6b**·Li moieties. Macroscopic H atoms omitted for clarity; hydrogen bonds indicated by dashed lines and Li⁺ coordination by open bonds.

carried out according to Scheme I with the 2-bromomagnesio derivatives. Although simple arenosulfonyl chlorides are relatively stable toward hydrolysis,¹⁵ we have only managed to isolate 2-(chlorosulfonyl)-1,3-xylyl-15-crown-4 (**5a**) by precipitation of the compound from the crude reaction mixture, by the addition of diethyl ether.

In the ¹H NMR spectrum of **5a**, the AB quartet of the benzylic protons, characteristic for most 2-substituted 1,3-xylyl-15-crown-4 ethers, indicates hindered inversion of the crown ether caused by the large SO_2Cl group. The structure of **5a** was determined by X-ray diffraction. From the view in Figure 1 it can be seen that the xylyl group is approximately perpendicular to the mean macrocyclic plane, with the chlorine of the SO_2Cl substituent residing above this plane. The structure shows no irregular features in the SO_2Cl moiety.¹⁷ The two S-O distances are 1.42 Å, the S-Cl distance is 2.05 Å. The chlorine is engaged in a short intermolecular contact with a C-H group: the C...Cl distance of 3.79 Å indicates a weak hydrogen bond,¹⁸ the C-H...Cl angle being 141° .

Hydrolysis of **5a** with water under neutral conditions is remarkably slow, even at 100°C , but complete hydrolysis of **5a** to **6a** can be achieved by refluxing **5a** in 2 N HCl. By contrast,

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Table I. Coordination Distances in the Crystal Structures of **6a**·H₂O, **6c**·(H₂O)₂, and **6e**·(H₂O)₃^a

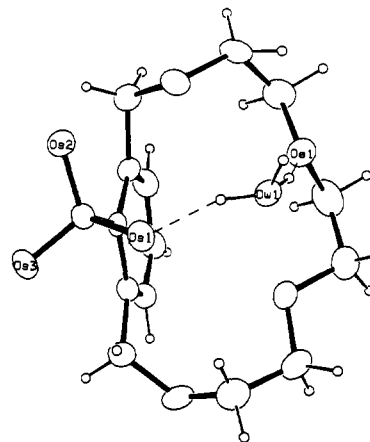
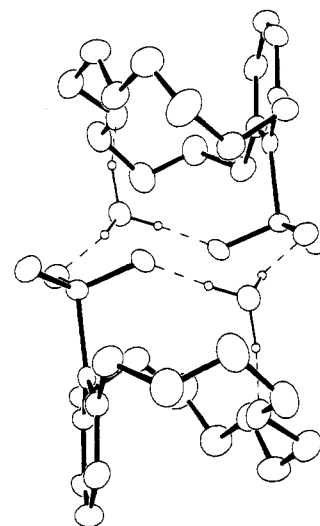
compd	6a ·H ₂ O	6c ·(H ₂ O) ₂	6e ·(H ₂ O) ₃
O...O Distances, Å			
O _{w1} ...O _{s1}	2.509 (3)	2.538 (6)	2.49 (1)
O _{w1} ...O _{s2}	2.544 (4)		
O _{w1} ...O _{w2}		2.443 (6)	2.41 (1)
O _{w1} ...O _{w3}			2.51 (1)
O _{w1} ...O _{e1}	2.603 (4)	2.662 (6)	
O _{w2} ...O _{e1}			2.70 (1)
O _{w2} ...O _{e2}		2.712 (6)	2.74 (1)
O _{w2} ...O _{e3}		2.727 (6)	
O _{w3} ...O _{e3}			2.86 (1)
O _{w3} ...O _{e4}			2.83 (2)
O...Coordination Plane Distance, ^b Å			
O _{w1} ...3 oxygens	0.539 (3)	0.691 (6)	0.63 (1)
O _{w1} ...3 hydrogens	0.27 (5)	0.42 (10)	^c
O _{w2} ...3 oxygens		0.834 (6)	0.62 (1)
O _{w3} ...3 oxygens			0.52 (1)
S-O Distances, Å			
S-O _{s1}	1.471 (3)	1.462 (5)	1.45 (1)
S-O _{s2}	1.462 (3)	1.435 (5)	1.50 (1)
S-O _{s3}	1.439 (2)	1.438 (4)	1.38 (1)

^aSubscripts s, w, and e indicate sulfonate, water (or hydronium), and ether oxygens, respectively, numbered as shown in Figures 4, 6, and 7. ^bDistance to the mean plane of the three coordinating oxygen atoms (or the three bonded hydrogen atoms). ^cH atoms not located.

2-(chlorosulfonyl)-1,3-xylyl-18-crown-5 (**5b**) and -21-crown-6 (**5c**) hydrolyze easily when treated with water and they could not be isolated in a pure state after the standard workup procedure. In the case of the 18-membered crown ether we isolated from the aqueous phase the lithium salt of 2-sulfo-1,3-xylyl-18-crown-5 (**6b**·Li·H₂O) in 35% yield. The structure of **6b**·Li·H₂O was determined by X-ray diffraction. The view in Figure 2 reveals the tetrahedral coordination of the lithium cation, by the water and a sulfonate oxygen at short distances of 1.87 and 1.90 Å, respectively, and by two ether oxygens at longer distances (2.01 and 2.09 Å). In this complex, as in the urea complex of 2,6-pyrido-27-crown-9-lithium perchlorate,^{6a} the lithium acts as a *super* proton, assisting in the complexation of a neutral molecule. The water molecule is also engaged in a short hydrogen bond (O...O distance, 2.72 Å; O-H...O angle, 167°) to a sulfonate oxygen of a second, symmetry-related, host molecule (see Figure 3). This gives rise to a polymeric structure in the crystal, with each water molecule bridging two **6b**·Li moieties, and vice versa. The second water hydrogen atom is involved in a nonlinear contact (O...O distance, 2.88 Å; O-H...O angle, 97°) with an ether oxygen (depicted as a hydrogen bond in Figures 2 and 3). In the sulfonate moiety, the S-O distances for the oxygens coordinated to water and lithium [1.455 (3) and 1.456 (2) Å, respectively] are longer than for the uncoordinated oxygen [1.441 (2) Å].

Apparently the hydrolysis of **5b** and **5c** is assisted by the macroring. The lithium salt of **6b** was converted into the sulfonic acid by treatment with concentrated HCl. **5c** hydrolyzed readily during the workup of the reaction mixture, after which we isolated from the organic phase crystals of 2-sulfo-1,3-xylyl-21-crown-6 (**6c**) as a very stable dihydrate. The larger 2-sulfo-1,3-xylyl crown ethers **6d-g** were obtained directly from the crude reaction mixtures by hydrolysis with 2 N HCl for 30 min.

All 2-sulfo-1,3-xylyl crown ethers **6** are extremely hygroscopic, and in the ¹H NMR spectra the absorption of -SO₃H·*n*H₂O was always observed. Since we have isolated previously water complexes of 2-carboxy-1,3-xylyl crown ethers^{6c} and of pyridinium crown ethers,¹⁰ we assumed that in the macrocyclic cavities of **6** water was also complexed. In three cases (**6a**, **6c**, and **6e**) we were able to isolate crystalline compounds that could be studied by single-crystal X-ray diffraction. This revealed that in all three cases the proton is transferred from the sulfonic acid group to a water molecule (**6a**), a water dimer (**6c**), or a water trimer (**6e**), respectively. Data on the coordination in the crystal structures are summarized in Table I.

**Figure 4.** Crystal structure of **6a**·H₂O, with the numbering of oxygen atoms involved in hydrogen bonding. Hydrogen bonds indicated by dashed lines.**Figure 5.** Crystal structure view of the dimer of **6a**·H₂O. Macrocyclic H atoms omitted for clarity; hydrogen bonds indicated by dashed lines.

In the structure of **6a**·H₂O (Figure 4), proton transfer is clearly observed, as the hydrogen atoms involved have been located unambiguously near the water oxygen. This charge separation results in strong, short hydrogen bonds between the positively charged hydronium and negative sulfonate oxygens or a neutral ether oxygen. The O...O distances agree with the average value of 2.57 Å, reported for hydrogen bonds of hydronium with oxygen atoms.¹⁹ For the ether oxygen the distance of 2.60 Å to the hydronium oxygen is short compared to the values of 2.8–3.0 Å for hydrogen bonds donated by neutral water molecules,¹⁰ indicating the shortening of hydrogen bonds due to the presence of a positive charge. The O-H...O angles (164–167°) point to almost linear hydrogen bonds. The hydronium ion is hydrogen bonded to sulfonate oxygens of two symmetry-related host molecules, which results in dimer formation (see Figure 5). This demonstrates a preference of the hydronium for a sulfonate over an ether oxygen.

In the structure of **6c**·(H₂O)₂ (Figure 6), a water molecule is hydrogen bonded to a sulfonate and an ether oxygen, and to a second water molecule, which in turn is bonded to two ether oxygens in the macrocyclic cavity. Direct proof of proton transfer is not clear. The proton involved has been refined with very low precision to a position approximately midway between a sulfonate oxygen and the water oxygen. Indirect proof, however, is present for proton transfer and the accompanying charge separation. First, the distance between the two water oxygens in the cavity is very

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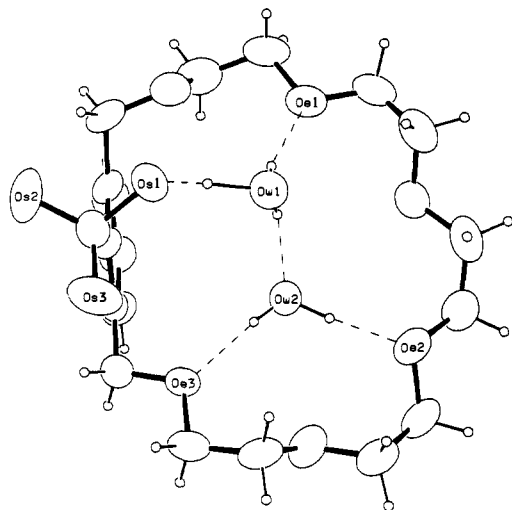


Figure 6. Crystal structure of $6c \cdot (H_2O)_2$, with the numbering of oxygen atoms involved in hydrogen bonding. Hydrogen bonds indicated by dashed lines.

short (2.44 Å), compared to the value of 2.90 Å found for a neutral water dimer in similar surroundings.¹⁰ In ice the shortest O...O distances are 2.75 Å.²⁰ Second, the O...O distances in the hydrogen bonds between water and ether oxygens (2.66–2.73 Å) are short.¹⁰ It is not clear whether the dimer must be viewed as a symmetric $H_5O_2^+$ moiety or as an asymmetric $H_3O^+ \cdot H_2O$. The positions of the hydrogen atoms seem to favor this last possibility; the accuracy, however, is very low. The short distances between the supposedly neutral water molecule and two ether oxygens indicate at least some charge (proton) delocalization over the two water molecules.

In the structure of $6e \cdot (H_2O)_3$ (Figure 7), a water molecule is coordinated in the macrocyclic cavity to a sulfonyl oxygen and to another two water molecules, which in turn are both at short distances from two ether oxygens. Hydrogen atoms have been located in hydrogen-bonding positions between the two water oxygens and the ether oxygens, but not near the central water oxygen. The distances between the central and the two outer water oxygens are again short, and in agreement with an average value of 2.48 Å, reported for $H_7O_3^+$ species,¹⁹ which means that in this case proton transfer is also very likely. According to the difference in these two distances (2.41 vs 2.51 Å for O_{w2} and O_{w3} , respectively) and in the corresponding distances of the water to the ether oxygens (2.70–2.74 vs 2.83–2.86 Å for O_{w2} and O_{w3} , respectively), this $H_7O_3^+$ ion is not symmetrical. However, for this complex the rather low accuracy does not allow definite conclusions.

Structural studies of complexation of neutral molecules by crown ethers have resulted in numerous crystal structures of crown-water complexes. In these complexes, the water hydrogens are engaged in hydrogen bonds with ether oxygens. The water oxygen is coordinated to an external acid, in a ternary complex,²¹ or to an intraannular acidic, hydrogen bond donating group.^{6,10,22} A metal cation can also assist in the complexation.^{5,23} In a few cases proton transfer from an external acid to a water molecule has been observed, resulting in a hydronium ion. Complexes of unsubstituted or tetracarboxylic 18-crown-6 with the hydronium

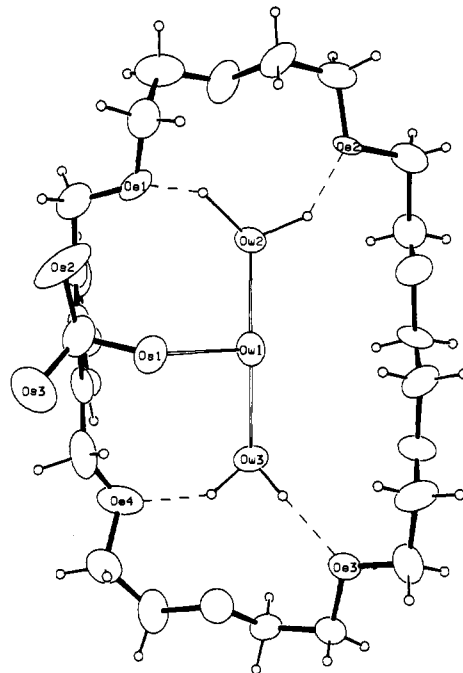


Figure 7. Crystal structure of $6e \cdot (H_2O)_3$, with the numbering of oxygen atoms involved in hydrogen bonding. Hydrogen bonds indicated by dashed lines; coordination of hydronium (no H atoms located) indicated by open bonds.

ion have been reported.²⁴ In water complexes of sulfonyl-containing compounds, proton transfer also has been observed.²⁵ Often these hydronium complexes contain additional water molecules solvating the charged species. The present work is, to our knowledge, the first example of a combination of these phenomena: complexation of water by a crown ether via proton transfer from an intraannular (sulfonic) acid group to a water molecule encapsulated in the macrocyclic cavity with additional water molecules.

A question that was addressed in the course of this work concerned the geometry of the hydronium ion, formed upon proton transfer to a water molecule. There has been much debate²⁶ as to whether the hydronium geometry (i.e., the position of the central oxygen relative to the plane of the three attached hydrogen atoms) is *planar* or *pyramidal*. Ab initio calculations have supported one or the other geometry, but recent results seem to favor the pyramidal geometry.^{26a} X-ray crystal structure determinations have also supported both alternatives, but often a decisive answer cannot be given, because of problems in locating the hydrogen atoms involved or due to crystallographic disorder.^{24b,c} However, solid-state data also tend to favor the pyramidal geometry,^{19,24a,25a} although recently a planar structure was postulated.^{24c}

The geometry of the hydronium ion is most clearly observed in the structure of $6a \cdot H_2O$ (see Table I). The oxygen atom is displaced by 0.27 Å from the mean plane of the three hydrogen atoms, resulting in a pyramidal geometry. Similar values of approximately 0.3 Å have been found.^{24a,25} The distance of the hydronium oxygen to the mean plane of the three coordinating oxygen atoms is 0.54 Å, which points to a pyramidal coordination. For $6c \cdot (H_2O)_2$ the corresponding values are even larger, but less accurate. In all three hydronium complexes, for all water and

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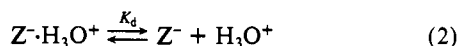
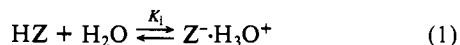
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hydronium oxygens the distance to the mean plane of their three coordinating oxygen atoms is in the range 0.5–0.8 Å. Behr and co-workers^{24a} report a value of 0.61 Å for a hydronium ion in the cavity of a crown ether. On the basis of our results, the hydronium ion, formed upon proton transfer in the complexes of **6** with water, clearly has a pyramidal geometry.

In the sulfonate moiety, slight differences are observed in the S–O distances for coordinated and uncoordinated oxygen atoms (see Table I), as was the case in the structure of **6b**·Li·H₂O (vide supra). For sulfonate oxygens accepting a hydrogen bond, the S–O distance is 1.46–1.47 Å, whereas for uncoordinated oxygens, values of 1.43–1.44 Å are found. The values for **6e**·(H₂O)₃ deviate from these averages, probably owing to the poor data quality.

In our work on pyridinium¹⁰ and 2-carboxy-1,3-xylyl⁶ crown ethers, we have found that the p*K*_a value of the intraannular acidic group is an indication of the encapsulation of a solvent or guest molecule. When we determined the p*K*_a values of **6a–g** in water by potentiometric titrations with perchloric acid, we found a surprisingly small variation of the p*K*_a as a function of the ring size of **6**. From the 15- to 33-membered ring there is a gradual decrease from 2.5 to 2.0. In the absolute sense these values are also surprising because in the literature much lower p*K*_a values of arenosulfonic acids have been reported (–2.8 for benzenesulfonic acid).²⁷ Therefore we must conclude that the apparent acidity of the 2-sulfo-1,3-xylyl crown ethers is much lower than we would expect when the macroring would be absent. Although in principle this could be due to complexation of water, which stabilizes the acidic form and not the anion, as we have found for pyridinium and 2-carboxy-1,3-xylyl crown ethers, there may well be a different explanation, as indicated by the solid-state structures.

It is generally accepted that the proton dissociation process of acids in water involves two steps, the ionization and the dissociation step:²⁷



When the value of *K*₂ is low, it is possible that a potentially strong acid does not release the equivalent [H₃O⁺]. As already shown for the solid state, the (solvated) H₃O⁺·(H₂O)_{*n*} ion (*n* = 0–2) fits nicely in the respective molecular cavities. When this would, to some extent, also be the case in aqueous solution, this would enlarge the concentration of the ion pair, [6·H₃O⁺·(H₂O)_{*n*}], and the lower acidity can be accounted for. Since cocomplexation of H₂O with H₃O⁺ may occur, we can explain why the p*K*_a values vary only slightly with the ring size. Kolthoff et al.²⁸ have determined the stability constants of complexes of hydronium ions with simple crown ethers such as 18-crown-6, in acetonitrile. They reported a log *K*[†] of 6.4 for the complex of H₃O⁺ and 18-crown-6. To our knowledge these stability constants have not been determined in water, but since several complexes of H₃O⁺ and simple macrocyclic polyethers have been isolated as the perchlorate²⁹ or tetrafluoroborate³⁰ salts, they may be comparable with the thermodynamic stabilities of complexes of ammonium³ and guanidinium³¹ cations.

The unexpectedly low “bulk” acidities of **6** would be in agreement with the complexation of H₃O⁺ in the molecular cavity as a special form of a tight ion pair which undergoes only partly dissociation (low value of *K*₂). However, the *microacidity*, defined as the free energy of proton transfer toward neutral guests other than solvent molecules, might be much larger. This *microacidity* is important in the complexation of neutral molecules and further

work in this direction is in progress. Preliminary results indicate that the larger 2-sulfo-1,3-xylyl crown ethers are excellent receptor molecules for urea. Both **6f** and **6g** solubilize 1 equiv of urea in chloroform.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ¹H NMR spectra (CDCl₃) were recorded with a Bruker WP-80 spectrometer, and ¹³C NMR spectra were recorded with a Nicolet NT 200 spectrometer (Me₄Si as an internal standard). Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer.

Materials. *n*-BuLi in *n*-hexane (Merck) was titrated with 2-butanol in the presence of 1,10-phenanthroline to determine its concentration.³² Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl before use. Diethyl ether and hexane were distilled from CaH₂ and stored over 4-Å molecular sieves. 2-Bromo-1,3-xylyl-3*n*-crown-(*n*–1) and 2-sulfo-1,3-xylyl-3*n*-crown-(*n*–1) ethers were prepared as previously described.¹⁴ Most other compounds used were commercially available unless stated otherwise. All reactions were carried out under a nitrogen atmosphere.

Synthesis of 2-Sulfo-1,3-xylyl-3*n*-crown-(*n*–1) Ethers. General Procedure. To a solution of 1.5 mmol 2-bromo-1,3-xylyl crown ether **1** in 5 mL of THF was added 1.1 equiv of *n*-butyllithium (1.5 M in hexane) slowly at –78 °C. After the reaction mixture was stirred 2 h at –78 °C, 2.6 mmol (1 mL) of freshly prepared solution of MgBr₂ in Et₂O was added.¹⁶ The reaction mixture was stirred 3 h at –78 °C, slowly warmed to –30 °C, and subsequently added to the stirred solution of 10 mmol (1 mL) of freshly distilled SO₂Cl₂ in 10 mL of dry hexane at –30 °C. The reaction mixture was stirred 2 h at room temperature and subsequently the solvents and an excess of SO₂Cl₂ were carefully evaporated in vacuo. The oily residue containing 2-(chlorosulfonyl)-1,3-xylyl crown ether **5** was solved in CHCl₃ (50 mL) and washed with water (3 × 5 mL) to remove salts, and the organic layer was dried over MgSO₄. After evaporation of the solvent, the remaining brown oil was (with an exception for 18- and 21-membered crown ethers) directly hydrolyzed with 20 mL of 2 N HCl, by stirring the reaction mixture at reflux temperature during 30 min. After cooling, the water phase was washed with chloroform (2 × 5 mL) and subsequently water was slowly evaporated under vacuo (the temperature of the solution did not rise above 60 °C). The residual yellowish oil of **6** was dried under vacuo and solved in CHCl₃, and the solution was dried over MgSO₄. After evaporation of the solvent, 2-sulfo-1,3-xylyl-3*n*-crown-(*n*–1) ether was obtained as an oil.

2-Sulfo-1,3-xylyl-15-crown-4 (6a): yield 50%; mp 84–88 °C (CH₂Cl₂); mass spectrum, *m/e* 332.082 (M⁺, calcd for C₁₄H₂₀O₇S 332.093); ¹H NMR δ 3.2–3.8 (m, 12 H, OCH₂), 4.33 and 5.87 (AB q, *J*_{AB} = 13.2 Hz, 4 H, ArCH₂), 5.4 (br s, SO₃H·*n*H₂O), 7.45 (s, 3 H, ArH); ¹³C NMR δ 68.4–72.5 (t, OCH₂), 131.4 and 131.5 (d, Ar C-4, C-5, and C-6), 140.6 (s, Ar C-1 and C-3).

2-Sulfo-1,3-xylyl-18-crown-5 (6b) was obtained from its lithium salt (**6b**·Li·H₂O), isolated as described below. To the suspension of 120 mg of **6b**·Li·H₂O in 5 mL of chloroform was added 30 μL of concentrated HCl, and the mixture was shaken 24 h at room temperature. Subsequently, an additional 50 mL of chloroform was added, and the solution was dried over MgSO₄. After evaporation of the solvent, **6b** was obtained as a colorless oil, slowly crystallizing on standing: yield 97%; mass spectrum, *m/e* 376.110 (M⁺, calcd for C₁₆H₂₄O₈S 376.119); ¹H NMR (200 MHz) δ 3.5–3.8 (m, 16 H, OCH₂), 4.37 and 5.84 (AB q, *J*_{AB} = 10.7 Hz, 4 H, ArCH₂), 6.99 (br s, SO₃H·*n*H₂O), 7.39 (s, 3 H, ArH); ¹³C NMR δ 68.1–72.6 (t, OCH₂), 130.8 (d, Ar C-5), 131.9 (d, Ar C-4 and C-6), 138.3 (s, Ar C-1 and C-3), 141.3 (s, Ar C-2); IR (KBr) 3380 cm^{–1} (OH).

2-(Lithiosulfonyl)-1,3-xylyl-18-crown-5 (6b·Li) was isolated from water phase, formed during workup of the crude solution of 2-(chlorosulfonyl)-1,3-xylyl-18-crown-5 in chloroform (see general procedure). After evaporation of water, the yellowish oil, slowly crystallizing on standing, was refluxed with 5 mL of THF and a droplet of water to form white crystals of **6b**·Li·H₂O: yield 35%; mp 120 °C dec; ¹H NMR (200 MHz) δ 2.5 (br s, 2 H, H₂O), 3.4–3.8 (m, 12 H, OCH₂), 4.0–4.15 (m, 4 H, OCH₂), 4.29 and 6.02 (AB q, *J*_{AB} = 9 Hz, 4 H, ArCH₂), 7.34 (s, 3 H, ArH); ¹³C NMR δ 68.1–73.3 (t, OCH₂), 129.9 (d, Ar C-5), 133.3 (d, Ar C-4 and C-6), 136.5 (s, Ar C-1 and C-3). Anal. Calcd for C₁₆H₂₅O₉SLi (*M*_r): C, 48.0; H, 6.29. Found: C, 47.97; H, 6.23.

2-Sulfo-1,3-xylyl-21-crown-6 (6c) was isolated without additional hydrolysis of crude reaction mixture with 2 N HCl (see general procedure) by stirring the oily residue obtained after typical workup of the reaction mixture with 20 mL of diethyl ether. White crystals precipitated

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Table II. Crystal Data and Data Collection Parameters

	compd				
	5a	6b·Li·H ₂ O	6a·H ₂ O	6c·(H ₂ O) ₂	6e·(H ₂ O) ₃
formula	C ₁₄ H ₁₉ O ₆ SCl	C ₁₆ H ₂₅ O ₉ SLi	C ₁₄ H ₂₂ O ₈ S	C ₁₈ H ₃₂ O ₁₁ S	C ₂₂ H ₄₂ O ₁₄ S
fw	350.82	400.38	350.39	456.51	562.64
lattice type	orthorhombic	orthorhombic	monoclinic	monoclinic	monoclinic
space group	<i>Pbca</i>	<i>P2₁2₁2₁</i>	<i>P2₁/n</i>	<i>P2₁/n</i>	<i>Pn</i>
T, K	167	176	167	293	168
cell dimensions					
<i>a</i> , Å	10.021 (4)	8.474 (1)	9.636 (2)	8.405 (3)	8.767 (2)
<i>b</i> , Å	13.257 (4)	13.567 (2)	16.380 (7)	21.510 (6)	10.651 (2)
<i>c</i> , Å	23.449 (8)	16.028 (4)	10.269 (2)	12.077 (4)	14.811 (6)
β , deg			94.87 (2)	95.17 (2)	96.01 (3)
<i>V</i> , Å ³	3115 (3)	1843 (1)	1615 (1)	2175 (2)	1375 (1)
<i>Z</i>	8	4	4	4	2
<i>D_c</i> , g cm ⁻³	1.50	1.44	1.44	1.39	1.36
<i>F</i> (000)	1472	848	744	976	604
μ , cm ⁻¹	4.0	2.1	2.3	1.9	1.7
θ -range, deg	3–25	3–27.5	3–25	3–25	3–25
no. of unique reflns					
measd	2724	2398	2827	3812	2427
obsd	1820	1733	1500	1262	1592
no. of variables	276	345	296	292	324
<i>R</i> , %	2.9	3.1	3.9	4.4	9.9
<i>R_w</i> , %	3.8	3.8	4.8	6.0	12.2
weighting factor <i>p</i>	0.05	0.06	0.05	0.08	0.04
extinction <i>g</i> (×10 ⁻⁷)	1.2 (3)	4.2 (12)	0.0	2.7 (8)	0.0

and were filtered and identified as **6c**·(H₂O)₂; yield 42%; mp 72–74 °C (CH₂Cl₂); mass spectrum, *m/e* 420.145 (M⁺, calcd for C₁₈H₂₈O₉S 420.145); ¹H NMR δ 3.58 and 3.70 (s, 20 H, OCH₂), 5.05 (s, 4 H, ArCH₂), 6.86 (br s, SO₃H·*n*H₂O), 7.4 (s, 3 H, ArH); ¹³C NMR δ 69.0–71.9 (t, OCH₂), 130.8 (d, Ar C-5), 132.5 (d, Ar C-4 and C-6), 137.3 (s, Ar C-1 and C-3), 140.5 (s, Ar C-2); IR (KBr) 3420 cm⁻¹ (OH).

2-Sulfo-1,3-xylyl-24-crown-7 (6d): yield 47% (oil); mass spectrum, *m/e* 464.163 (M⁺, calcd for C₂₀H₃₂O₁₀S 464.172); ¹H NMR δ 3.5–3.8 (m, 24 H, OCH₂), 4.95 (s, 4 H, ArCH₂), 7.46 (s, 3 H, ArH), 8.19 (br s, SO₃H·*n*H₂O); ¹³C NMR δ 69.4–72.2 (t, OCH₂), 130.8 (d, Ar C-5), 132.4 (d, Ar C-4 and C-6), 136.3 (s, Ar C-1 and C-3), 141.1 (s, Ar C-2); IR (KBr) 3400 cm⁻¹ (OH).

2-Sulfo-1,3-xylyl-27-crown-8 [6e·(H₂O)₃]: yield 51%; mp 62–64 °C (CH₂Cl₂/Et₂O); mass spectrum, *m/e* 508.193 (M⁺, calcd for C₂₂H₃₆O₁₁S 508.198); ¹H NMR δ 3.5–3.8 (m, 28 H, OCH₂), 5.07 (s, 4 H, ArCH₂), 7.3–7.6 (m, 3 H, ArH), 8.29 (br s, SO₃H·*n*H₂O); ¹³C NMR δ 69.7–71.7 (t, OCH₂), 130.2 (d, Ar C-4 and C-6), 130.7 (d, Ar C-5), 137.3 (s, Ar C-1 and C-3), 139.3 (s, Ar C-2); IR (KBr) 3420 cm⁻¹ (OH).

2-Sulfo-1,3-xylyl-30-crown-9 (6f): yield 49% (oil); mass spectrum, *m/e* 552.226 (M⁺, calcd for C₂₄H₄₀O₁₂S 552.224); ¹H NMR δ 3.6–3.8 (m, 32 H, OCH₂), 5.04 (s, 4 H, ArCH₂), 7.4–7.7 (m, 3 H, ArH), 9.13 (br s, SO₃H·*n*H₂O); ¹³C NMR δ 69.6–71.7 (t, OCH₂), 130.0 (d, Ar C-4 and C-6), 131.1 (d, Ar C-5), 137.8 (s, Ar C-1 and C-3), 138.3 (s, Ar C-2); IR (KBr) 3420 cm⁻¹ (OH).

2-Sulfo-1,3-xylyl-33-crown-10 (6g): yield 47% (oil); mass spectrum, *m/e* 596.240 (M⁺, calcd for C₂₆H₄₄O₁₃S 596.250); ¹H NMR δ 3.6–3.8 (m, 36 H, OCH₂), 5.05 (s, 4 H, ArCH₂), 7.2 (br s, SO₃H·*n*H₂O), 7.4–7.7 (m, 3 H, ArH); ¹³C NMR δ 69.7–71.7 (t, OCH₂), 129.7 (d, Ar C-4 and C-6), 130.6 (d, Ar C-5), 137.4 (s, Ar C-1 and C-3), 139.1 (s, Ar C-2); IR (KBr) 3400 cm⁻¹ (OH).

2-(Chlorosulfonyl)-1,3-xylyl-15-crown-4 (5a) was partly isolated from the crude oily residue, obtained from **1a** after evaporation of chloroform (see general procedure), by trituration with diethyl ether. The precipitated white crystals were filtered, washed with small amount of diethyl ether, and identified as **5a**: mp 140–142 °C; mass spectrum, *m/e* 315.090 (M⁺ - Cl, calcd for C₁₄H₁₉O₆S 315.090); ¹H NMR δ 2.8–4.0 (m, 12 H, OCH₂), 4.71 and 5.49 (AB q, *J*_{AB} = 14.9 Hz, 4 H, ArCH₂), 7.64 (s, 3 H, ArH); ¹³C NMR δ 70.7–73.4 (t, OCH₂), 129.2 (d, Ar C-4 and C-6), 133.2 (d, Ar C-5), 142.1 (s, Ar C-1 and C-3).

2-[(*N*-Isopropylamino)sulfonyl]-1,3-xylyl-27-crown-8 (7e) was prepared from **1e** by addition of 0.7 mL (8.2 mmol) of isopropylamine to the crude residue of **5e**, obtained after evaporation of the solvents and an excess of SO₂Cl₂ (see general procedure), and redissolved in 7 mL of THF. The reaction mixture was stirred at room temperature for 1 h. After evaporation of the solvents, the residue was solved in 50 mL of CHCl₃ and washed with water (3 × 25 mL), and the organic phase was dried over MgSO₄. The crude product was purified by column chromatography on alumina with petroleum ether (60–80)/chloroform (60/40, v/v) and subsequently on silica gel with ethanol/ethyl acetate (5/95, v/v). The colorless oil, slowly crystallizing on standing, was

trituated with diethyl ether: yield 48%; mp 90–91.5 °C; mass spectrum, *m/e* 549.259 (M⁺, calcd for C₂₅H₄₃NO₁₀S 549.261); ¹H NMR δ 1.1 (d, *J* = 6.6 Hz, 6 H, CH₃), \approx 2 (br m, 1 H, CH), 3.5–3.75 (m, 28 H, OCH₂), 5.04 (s, 4 H, ArCH₂), 5.93 (br d, 1 H, NH), 7.5–7.75 (m, 3 H, ArH); ¹³C NMR δ 23.8 (q, CH₃), 45.8 (d, CH), 69.9–72.2 (t, OCH₂), 130.8 (d, Ar C-4 and C-6), 131.8 (d, Ar C-5), 138.1 (s, Ar C-1 and C-3), 138.3 (s, Ar C-2).

pK_a Measurements. Determinations of the pK_a's²⁷ were carried out in nitrogen-flushed solvents in a thermostated titration vessel at 25.0 °C by means of a computerized potentiometric titration device. Detailed information on the apparatus used is described elsewhere.³³ Titrants were 0.03–0.10 M solutions of tetrabutylammonium and tetramethylammonium hydroxide. At least 15 relevant data points within 1 pH unit from the pK_a were used for the calculation of the pK_a. Between every (fixed) titrant addition, there was a waiting time of at least 45 s in which the pH did not vary more than 0.02 unit. Since the concentrations of titrands were low (<0.005 mol dm⁻³), no corrections for the activities of the species were made in the calculations. After every third run, the glass/silver–silver chloride electrode combination (Metrohm, Type EA121, 6.0203.000) was calibrated. At least three standard (Merck) buffer solutions in the relevant pH section were used. The pK_a determinations were performed at least in duplicate and generally showed a good agreement. All calculations were performed with the SUPERQUAD computer program.³⁴

X-ray Crystallography. X-ray diffraction measurements were performed on an Enraf-Nonius CAD4 diffractometer, using graphite-monochromated Mo K α radiation. Crystal data and data collection parameters are in Table II. Lattice parameters were determined by least squares from 22–25 centered reflections. Intensities were measured in the $\omega/2\theta$ scan mode and corrected for the decay of three control reflections, measured every hour, and for Lorentz-polarization effects.

The structures were solved by direct methods.³⁵ Reflections with $F_o^2 > 3\sigma(F_o^2)$ were considered observed and included in the refinement (on *F*) by full-matrix least squares; weights were calculated as $w = 4F_o^2 / \sigma^2(F_o^2)$, $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$, $\sigma(I)$ based on counting statistics and *p* an instability factor obtained from plots of *F_o* vs weighted error. After completion of the isotropic refinement of the non-H atoms an empirical absorption correction, using the DIFABS³⁶ routine, was performed for all structures. Not all H atoms could be located on difference Fourier maps of the structures. For **5a**, **6b**·Li·H₂O, and **6a**·H₂O, all H atoms were located and included in the refinement. For **6c**·(H₂O)₂, H atoms were located or put in reasonable positions and then included in the refinement.

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For $6e\cdot(H_2O)_3$, no H atoms were located near the central water oxygen; H atoms in hydrogen bonds of water with ether oxygens were found on a final difference Fourier map. For $6c\cdot(H_2O)_2$ and $6e\cdot(H_2O)_3$, macrocyclic H atoms were put in calculated positions and treated as riding on their parent C atoms. Further details concerning the treatment of the H atoms are in the supplementary material. For $6e\cdot(H_2O)_3$, two C atoms could not be refined anisotropically, due to the poor data quality. Parameters refined were the overall scale factor, an isotropic extinction parameter $g \{F_o = F_c / (1 + gI_c)\}$, positional and anisotropic thermal parameters for non-H atoms, and positional and isotropic thermal parameters for H atoms. Although for $6c\cdot(H_2O)_2$ and $6e\cdot(H_2O)_3$ the macrocyclic H atoms were not refined independently, the data-to-variable ratio was still rather low. Refinement converged with shift/error ratios less than unity. Final difference Fourier maps showed no significant features, except the peaks for $6e\cdot(H_2O)_3$ near two water oxygens, which were assumed to be H atoms. All calculations were done with SDP.³⁷

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Views of the structures, showing 50% probability thermal ellipsoids for non-H atoms and spheres of arbitrary size for H atoms, were produced with ORTEP.³⁸

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Supplementary Material Available: ORTEP drawings and tables of positional and thermal parameters of all atoms, bond distances and angles, and torsion angles in the macrocycle, for the crystal structures of compounds **5a**, **6b**·Li·H₂O, **6a**·H₂O, **6c**·(H₂O)₂, and **6e**·(H₂O)₃ (23 pages). Ordering information is given on any current masthead page.

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Resolution of Benzophenone Delayed Fluorescence and Phosphorescence Spectra. Evidence of Vibrationally Unrelaxed Prompt Benzophenone Fluorescence¹

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Abstract: Resolution of the delayed fluorescence and phosphorescence spectra of benzophenone was achieved by application of principal component analysis combined with a self-modeling technique on a set of benzophenone emission spectra from degassed carbon tetrachloride solutions in the -2.4 to 85.2 °C temperature range. The temperature dependence of the quantum yield ratio of the two emissions gives $\Delta H = 6.3 \pm 0.3$ kcal/mol which, though significantly higher than previous estimates, is in excellent agreement with the spectroscopic S_1 - T_1 splitting. Calculation of $k_f = 1.1 \pm 0.1 \times 10^6$ s⁻¹ for the radiative fluorescence rate constant with the Birks-Dyson equation allows estimation of $\Delta S = 0.73 \pm 1.0$ gibbs/mol for triplet \rightleftharpoons singlet equilibration from the intercept of the van't Hoff plot. The positive value of ΔS together with the more diffuse vibrational structure of the fluorescence spectrum relative to the phosphorescence spectrum suggest a larger geometry change for the $S_1 \rightarrow S_0$ than for the $T_1 \rightarrow S_0$ transition. Substantial differences between our measured prompt fluorescence spectrum of benzophenone and the delayed fluorescence spectrum demonstrate that the short S_1 lifetime prevents full relaxation of emitting benzophenone singlets. Differences between our prompt fluorescence spectrum and earlier time-resolved spectra are discussed.

Benzophenone is a widely used triplet energy donor and its photochemistry and photophysics have been thoroughly studied. Many years ago we demonstrated that excitation of benzophenone in CCl₄ solutions gives rise to emission which is composed mainly of delayed fluorescence (DF) and phosphorescence (P) originating from thermally equilibrated S_1 and T_1 states,² as reported earlier for benzophenone in the vapor phase.³ The observation of DF in solution⁴ and in rigid media⁵ was confirmed shortly thereafter in other laboratories.

The scheme in Figure 1 summarizes the kinetic processes of the lowest singlet and triplet excited states of benzophenone in

solution. The rate constants k_f , k_{is} , k_{-is} , k_p , and k_d represent fluorescence, intersystem crossing ($S_1 \rightarrow T_1$), back-intersystem crossing ($S_1 \leftarrow T_1$), phosphorescence, and nonradiative triplet decay, respectively. Because the S_1 - T_1 energy gap is small and T_1 is relatively long-lived (~ 100 μ s in CCl₄), the two excited states reach thermal equilibrium at moderate temperatures.²⁻⁵ The severe overlap between DF and P spectra can also be attributed to the small S_1 - T_1 energy gap. A van't Hoff plot based on the assumption that emissions at 2.56 and 2.06 μ m⁻¹ consisted of pure DF and P, respectively, gave $\Delta H = 4.4$ kcal/mol.² A slightly larger value was obtained by using a benzophenone time-resolved fluorescence spectrum to subtract the contribution of fluorescence from the total 2.06- μ m⁻¹ luminescence intensity.⁴ Since a proper van't Hoff treatment of the temperature dependence of the luminescence spectra requires knowledge of the exact DF and P spectra, we undertook the resolution of the spectra by application of principal component analysis in combination with the self-modeling method (PCA-SM).¹ The successful resolution of the benzophenone DF and P spectra and a reinvestigation of benzophenone's prompt fluorescence (PF) are reported here.

Experimental Section

Materials. Benzophenone (Fischer, Certified Reagent) was twice recrystallized from hexane and then triply sublimed before use. Carbon

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