Intermolecular interactions of tetraanions of macrocyclic tetraresorcinol in H_2O—DMF solutions

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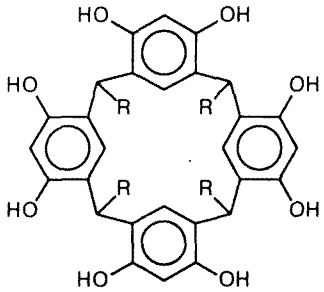
According to the data of pH-metric titration, macrocyclic tetraresorcinol (**1c**) dissociates stepwise with the abstraction of one, two, and four protons. Aggregation of tetraanions of **1c** in H_2O—DMF solutions was detected by conductometry. The degree of aggregation increases as the size of the counterion decreases and the content of DMF in the solvent mixture increases.

Key words: macrocyclic tetraresorcinol, dissociation, aggregation; quantum-chemical calculations, MNDO—PM3 method.

Researchers are interested in derivatives of tetraresorcinols (**1**) due to some of their features, including the ease of preparation and the high yield of the isomer in the "crown" conformation; the high solubility of tetraresorcinols containing bulky hydrophobic substituents (**1a,c**) in nonpolar solvents; their high capability of forming complexes both with cations[1,2] and with neutral molecules.[3–5]



1a—d

R = $C_{11}H_{23}$ (**a**), Me (**b**), C_7H_{15} (**c**), H (**d**)

Complexes of **1a** with dicarboxylic acids,[3] sugars,[4] and some polyols[5] have been detected by circular dichroism (CD) and by ^1H and ^{13}C NMR spectroscopy in chloroform. In more polar solvents, for example, in acetone and in a $CHCl_3$—MeOH mixture, these interactions do not occur. In polar solvents, compound **1b** dissociates with the abstraction of four protons, and the resulting tetraanion is not deprotonated even by the addition of 8 equiv. of NaOD or $NaOCD_3$ (see Refs. 1, 2). The authors cited[1,2] believe that this is due to the stabilization of the tetraanion in a so-called bowl-shaped structure through hydrogen bonds, and to the delocalization of the negative charge over the eight O atoms. The fact that the charge is equal to 4— and the presence of a fixed conformation favorable for complex formation accounts for the affinity of molecules of **1b** to bulky cations like R_4N^+.

Water-soluble calyx-arenes with hydrophilic rims and with R = C_6H_{13} or C_7H_{15} are known to be capable of forming micelles in polar media due to intermolecular hydrophobic interactions.[6] The purpose of the present work is to study the intermolecular interactions of tetraanions of macrocyclic tetraresorcinol **1c** in solutions in H_2O—DMF mixtures containing 80 and 50 % (v/v) DMF.

Experimental

Tetraresorcinol **1c** was prepared according to a previously described procedure[7] as an isomer with the *cis*-orientation of substituents R in a bowl-shaped conformation of the phenyl groups. The region of the maximum accumulation of the tetraanion in solution was determined from the data of pH-metric titration. The pH values were measured in temperature-controlled cells at 25±0.05 °C using an I-130 pH-meter. The contribution of the liquid potential to the pH in a water-organic medium was estimated by a known procedure.[8] Titration was carried out with KOH, because the use of bases incorporating smaller cations could lead to "sodium error" in the determination of pH values greater than 9, and the variation of the pH with an increase in the concentration of NR_4OH can be due not only to deprotonation but also to complex formation.[1,2] For the same reason, supporting neutral salts could not be used to maintain a constant ion strength in the solution. The results of the pH-metric titration were processed using the CPESSP program.[9]

The absorption spectra of compound **1c** were recorded on a Specord UV-Vis spectrometer in a 1 mm-thick cell. Quantum-

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chemical calculations were carried out using the AMPAC program[10] with full geometry optimization in the MNDO—PM3 parametrization.[11]

Results and Discussion

According to the published data, one may suggest that compound **1c** (H_8L) is deprotonated according to Eq. (1). However, the titration curve of **1c** in a H_2O—DMF mixture (20 : 80 (v/v)) exhibits more than one jump (Fig. 1, *b*), and its adequate description requires that equilibria (2) and (3) be included in the model of deprotonation.

$$H_8L \rightleftharpoons [H_4L]^{4-} + 4\,H^+ \qquad (1)$$

$$H_8L \rightleftharpoons [H_7L]^{-} + H^+ \qquad (2)$$

$$H_8L \rightleftharpoons [H_6L]^{2-} + 2\,H^+ \qquad (3)$$

$$H_2R \rightleftharpoons [R]^{2-} + 2\,H^+ \qquad (4)$$

The corresponding p*K* values for equilibria (1)—(3) are given in Table 1. The p*K* value for resorcinol (H_2R), which dissociates by Eq. (4), obtained under the same conditions is also given. Thus, according to the data of pH-metric titration, deprotonation of tetraresorcinol **1c**, unlike that of **1b**, in addition to equilibrium (1), includes also equilbria (2) and (3), the relative contributions of which are illustrated by Fig. 1, *a*. The p*K* values for the abstraction of the first two protons from molecule **1c** are smaller by approximately unity and those for the two subsequent protons are greater by approximately unity than the p*K* value for resorcine (see Table 1). The absorption spectrum of tetraresorcinol **1c** in DMF in the UV region is similar to the spectrum of resorcinol with a slight bathochromic shift of the maximum from 278 to 290 nm. The deprotonation of compound **1c** in H_2O—DMF solutions is accompanied by a bathochromic shift of the main

Table 1. p*K* values for the dissociation of tetraresorcinol H_8L (Eqs. (1)—(3)) and resorcinol (Eq. (4))

Equilibrium	p*K*	
	80 % (v/v) DMF	50 % (v/v) DMF
(1)	42.9±0.13	41.4±0.13
(2)	8.7±0.09	8.6±0.06
(3)	19.3±0.05	18.9±0.09
(4)	22.3±0.10	21.5±0.09

Note. The concentration of H_8L is 0.034 mol L^{-1}.

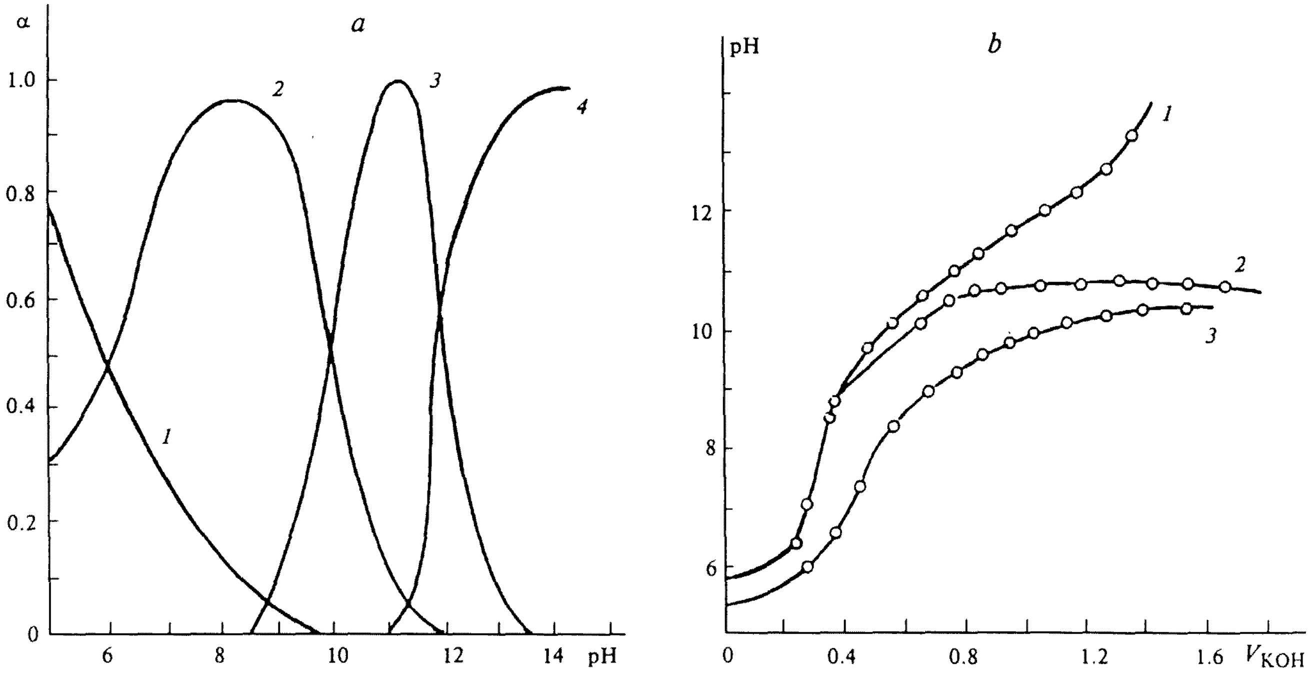

Fig. 1. *a*. Dependence of the accumulation (α) of tetraresorcinol **1c** in various degrees of deprotonation on the pH in a solution in a H_2O—DMF mixture (20 : 80 (v/v)): H_8L (*1*), $[H_7L]^-$ (*2*), $[H_6L]^{2-}$ (*3*), and $[H_4L]^{4-}$ (*4*).
b. Curves of the pH-metric titration of tetraresorcinol **1c** in a H_2O—DMF solution containing 80 % (v/v) DMF (*1*, *2*) and 50 % (v/v) DMF (*3*); [**1c**] = 0.0034 mol L^{-1}, [KOH] = 0.134 mol L^{-1}.

absorption band to 315 nm, and by the appearance of absorption at 370 nm, the intensity of which increases with increasing pH. The absence of an isobestic point precludes a quantitative processing of the pH dependence of the absorption intensity. The addition of $CsClO_4$ and R_4NI (R = Et, Bu) to a solution of tetraresorcinol **1c** in an H_2O—DMF mixture also leads to the appearance of an absorption band at 370 nm, which points to the formation of a complex between **1c** and the Cs^+ and R_4N^+ cations, accompanied by the abstraction of protons. An MNDO—PM3 calculations of the structure and the energy of interaction of tetraresorcinol **1d** and its di- and tetraanions with MeH_3N^+ showed that the tetraanion and the neutral form of **1d** incorporated in the complex have a symmetry close to C_4, and that the average distances between the N atom of the cation and the O atoms of the macrocycle are 4.9—5.0 Å and 5.1—5.2 Å, respectively. The hydroxyl protons in the tetraanion form hydrogen bonds with the neighboring O atoms (the $O \cdots O^-$ distance is 3.4 Å and the $O-H \cdots O^-$ angle is 167°). The energies of the formation of complexes between the neutral form, the dianion, and the tetraanion of **1d** and MeH_3N^+ in the gas phase are −71, −144, and −271 kcal mol^{-1}, respectively. Thus, according to the calculations, the maximum energy of complex formation corresponds to the tetraanion of **1d**. This is consistent with the experimental results obtained for a solution in a H_2O—DMF mixture (20 : 80 (v/v)). According to the pH-metric titration, Bu_4N^+ in the H_8L—Bu_4NI system forms complexes with both the dianion and the tetraanion (reactions (5) and (6)).

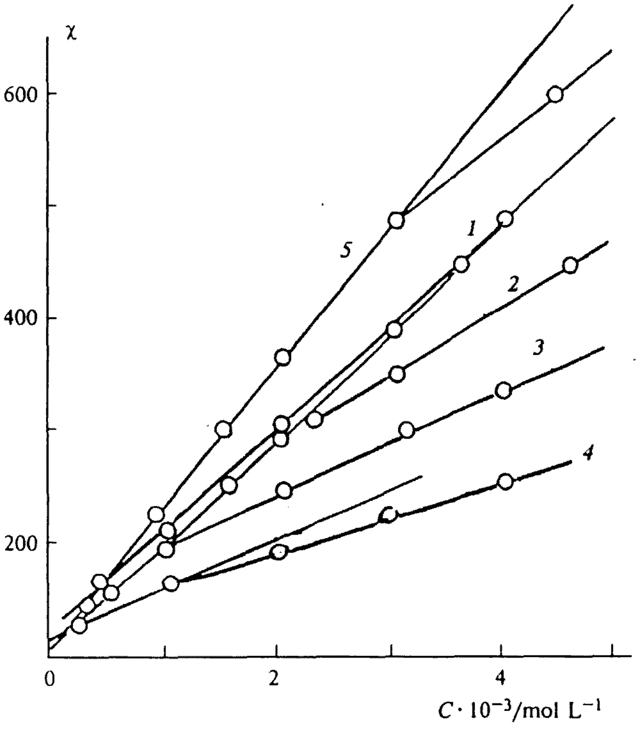

Fig. 2. Dependence of electrical conductivity (χ) on the concentration of M_4H_4L and on the nature of the counterion in a H_2O—DMF solution containing 80 % (v/v) DMF (*1—4*) and 50 % (v/v) DMF (*5*): M = $(Bu)_4N^+$ (*1*), K^+ (*2, 5*), Na^+ (*3*), and Li^+ (*4*).

$$Bu_4N^+ + [H_6L]^{2-} \rightleftharpoons [Bu_4NH_6L]^- \qquad (5)$$

$$Bu_4N^+ + [H_4L]^{4-} \rightleftharpoons [Bu_4NH_4L]^{3-} \qquad (6)$$

The logarithms of the stability constants of the above-mentioned complexes are 3.0 and 4.3, respectively.

An interesting feature of solutions of the tetraanion of **1c** in a H_2O—DMF mixture (20 : 80 (v/v)) is the time dependence of the results of the pH-metric titration (see Fig. 1, *b*) and of the intensity of the absorption band at 370 nm. In fact, the pH of the solution of the tetraanion decreases from 14 to 10.6 (see Fig. 1, *b*, curve *2*), and the intensity of the absorption at 370 nm increases. Similar variations of the pH-metric data occur as the proportion of water in the water-organic mixture increases. In fact, the curve of the pH-metric titration of tetraresorcinol **1c** in a H_2O—DMF mixture containing 50 % (v/v) DMF is characterized by the presence of a buffer region, instead of the jump expected on the addition of 4 equiv. of alkali (see Fig. 1, *a*, curve *3*), whereas the model of deprotonation does not change on going from 80 to 50 % (v/v) DMF in the system (see Table 1). Thus, the pH of the H_2O—DMF solution of the tetraanion of **1c** depends on the time and on the composition of the water-organic medium.

The presence of an inflection point in the dependence of the electrical conductivity (χ) of a solution of the tetraanion of **1c** in an H_2O—DMF mixture on the content of the latter (80 % (v/v) DMF) attests to an aggregation of species at a concentration of M_4H_4L (M = K) of $>2 \cdot 10^{-3}$ mol L^{-1} (Fig. 2). However, as time goes on (several hours), the electrical conductivity increases, which indicates that the aggregates are partially destroyed. When the content of DMF decreases from 80 to 50 % (v/v), the critical concentration of the aggregation (CCA) increases to $3 \cdot 10^{-3}$ mol L^{-1} (see Fig. 2). Thus, a decrease in the content of DMF also leads to partial destruction of the aggregates. A further factor having an effect on the physicochemical properties of the solution of the tetraanion is the nature of the counterion. It follows from Fig. 2 that in the presence of Bu_4N^+, the concentration dependence of χ exhibits no inflections and that the decrease in the size of the cation on going from K^+ to Na^+ and Li^+ leads to a decrease in the CCA. The electrical conductivity of solutions of M_4H_4L (M = Na and Li) does not change with time, which indicates that the aggregates formed are stable. Thus, the degree of aggregation of the tetraanion in H_2O—DMF solutions decreases as the size of the cation increases and also as the content of water in the mixture increases. However, whereas the time dependence of the electrical conductivity and of the absorption intensity is

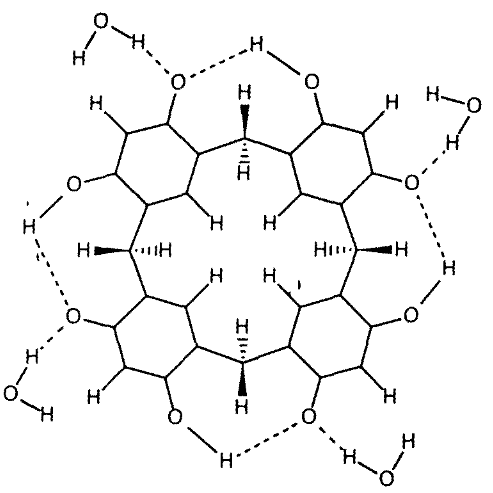

Fig. 3. Orientation of four H_2O molecules around the tetraanion of **1d**. MNDO—PM3 calculations.

manifested at concentrations of K_4H_4L exceeding the CCA, the decrease in the pH with time is not related to the aggregation processes, because it is also observed for solutions of M_4H_4L with concentrations lower than CCA.

The specific features of the solvation of the tetraanion in a H_2O—DMF mixture are due to the presence of the hydrophilic rim, which is predominantly hydrated, and of the hydrophobic cavity, which is solvated by DMF molecules, and this, in turn, has an effect on the structure of the water-organic solution. The MNDO—PM3 calculations of the interaction of tetraresorcinol **1d** and its tetraanion with four water molecules indicate that the complex of the latter is much more stable (ΔE = −76 kcal mol^{-1}) than the analogous complex of tetraresorcinol (ΔE = −7 kcal mol^{-1}). The structure of the complex of the tetraanion **1d** with four H_2O molecules is given in Fig. 3. The negatively charged O atoms participate in the formation of two hydrogen bonds. Since the water molecules are tightly held by the tetraanion, one may expect that the next layer of H_2O molecules would also be arranged rather rigidly around the tetraanion. In view of the fact that the ionization product of water ($pK_w = [H^+] \cdot [OH^-]$) depends substantially on the composition of the water-organic mixture and on the presence of salts, it is reasonable to expect that such a solvation of the tetraanion can lead to a variation of the pK_w and, consequently, of the pH.

Thus, we found by conductometry that aggregated species are formed in solutions of the tetraanion of **1c** in a H_2O—DMF mixture and the degree of aggregation of M_4H_4L increases as the size of the counterion decreases and as the concentration of DMF increases.

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