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THERMODYNAMIC IONIZATION CONSTANTS FOR CROWN ETHER CARBOXYLIC ACIDS IN AQUEOUS DIOXANE

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ABSTRACT

Thermodynamic ionization constants have been determined in 70% dioxane–water (by volume) for nine macrocyclic polyether (crown ether) compounds which have pendant carboxylic acid functions. The influence of structural variation within the crown ether carboxylic acid upon the thermodynamic ionization constant is assessed.

INTRODUCTION

Macrocyclic polyether (crown ether) compounds with ionizable side groups are novel ligands for the solvent extraction and transport of alkali metal and alkaline earth cations across liquid membranes [1–7]. Compared with their neutral analogs, such ionizable crown ethers have the important advantage that movement of a metal cation from the aqueous phase into an organic medium does not require concomitant transport of an aqueous phase anion [1]. This factor is of immense importance for potential practical applications of crown ether ligands in which such highly hydrophilic common anions as chloride, nitrate, and sulfate would be involved.

Recently, a variety of crown ethers with pendant carboxyl functions have been prepared [2,8–10]. Structural variation within the macrocyclic polyether unit and in the tether which links the polyether framework to the ionizable group strongly influence both the selectivity and efficiency of alkali metal and alkaline earth cation extraction and transport [1–7].

To provide greater insight into the factors which control metal ion complexation by ionizable crown ethers in solvent extraction and membrane

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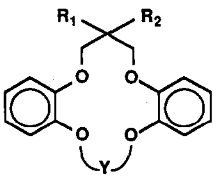
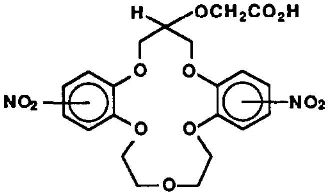


	R_1	R_2	Y
I	H	$-OCH_2CO_2H$	CH_2CH_2
II	H	$-OCH_2CO_2H$	$CH_2CH_2CH_2$
III	H	$-OCH_2CO_2H$	$CH_2CH_2OCH_2CH_2$
IV	H	$-OCH(C_2H_5)CO_2H$	$CH_2CH_2OCH_2CH_2$
V	H	$-O(CH_2)_4CO_2H$	$CH_2CH_2OCH_2CH_2$
VI	n-$C_{10}H_{21}$	$-OCH_2CO_2H$	$CH_2CH_2OCH_2CH_2$
VII	n-$C_{14}H_{29}$	$-OCH_2CO_2H$	$CH_2CH_2OCH_2CH_2$
VIII	H	$-OCH_2CO_2H$	$CH_2CH_2(OCH_2CH_2)_2$



IX

transport processes, thermodynamic ionization constants, $^{T}pK_a$, for nine crown ether carboxylic acids **I–IX** have now been determined. Although stoichiometric acid dissociation constants have been measured previously for ligands **I–V** and **VIII** [8,11], thermodynamic equilibrium constants for the dissociation of such ligands have not been reported. From a theoretical viewpoint, $^{T}pK_a$ is of greater value than a stoichiometric constant since the former defines interactions among the species in pure solvent; that is, each ion is free from the effect of all other species except the solvent molecules [12]. Since the crown ether carboxylic acids employed in this study are sparingly soluble in water, a mixed dioxane–water system was utilized for the measurements.

EXPERIMENTAL

Materials

Crown ether carboxylic acids **I–V** and **VIII** were prepared by literature procedures [8,9].

Ligands **VI** and **VII** were prepared by the following general procedure. Under nitrogen, 1.00 g (25.0 mmol) of sodium hydride (60% dispersion in mineral oil) was washed with dry pentane to remove the protecting mineral oil and was suspended in 200 ml of dry tetrahydrofuran. After 12.5 mmol of the appropriate *sym*-(alkyl)(hydroxy)dibenzo-16-crown-5 [9,13] was added, the mixture was stirred for 1 h. A solution of bromoacetic acid (1.64 g, 11.8 mmol) in 25 ml of dry tetrahydrofuran was added dropwise followed by stirring at 40°C for 48 h and refluxing for 2 h. Water (50 ml) was added to the cooled reaction mixture and the tetrahydrofuran was evaporated in vacuo. The resultant mixture was acidified to $pH = 1$ with 6 N HCl and extracted with dichloromethane (3×100 ml). The combined extracts were washed with water, dried over magnesium sulfate, and evaporated in vacuo to give the crude product which was purified by chromatography on silica gel with dichloromethane as eluent to give a white solid.

Compound **VI** was prepared in 82% yield and had a melting point of 102–102.5°C. IR (KBr, cm^{-1}): 3630–2280 (OH), 1766, 1740 (C=O), 1255, 1120 (CO). ^1H NMR ($CDCl_3$, δ): 6.89 (s, 8H), 5.0–3.6 (m, 14H), 1.9–0.8 (m, 21H). MS: 544.5 (M^+). Analysis calculated for $C_{31}H_{44}O_8$: C, 68.36; H, 8.14. Found: C, 68.07; H, 8.15.

Compound **VII** was prepared in 85% yield and had a melting point of 107–108°C. IR (KBr, cm^{-1}): 3400–2400 (OH), 1770, 1730 (C=O), 1255, 1120 (CO). ^1H NMR ($CDCl_3$, δ): 6.89 (s, 8H), 4.9–3.6 (m, 14H), 1.9–0.8 (m, 29H). Analysis calculated for $C_{35}H_{52}O_8$: C, 70.00; H, 8.67. Found: C, 70.12; H, 8.55.

For the preparation of compound **IX**, 1.3 ml of concentrated nitric acid, followed by 1.0 ml of water were added to a stirred solution of *sym*-(dibenzo-16-crown-5-oxy)acetic acid (1.00 g, 2.47 mmol) in 5.0 ml of glacial acetic acid and 5.0 ml of chloroform. Stirring was continued for 1 h and the reaction mixture was allowed to stand for 1 h before being poured into water (400 ml). The yellow solid was filtered and washed several times with water and dried in vacuo to give 1.20 g (99%) of **IX** with a melting point of 153–158°C. IR (KBr, cm^{-1}): 3340 (OH), 1720 (C=O), 1485, 1315 (NO_2), 1115 (CO). ^1H NMR (CD_3SOCD_3, δ): 8.5–7.0 (m, 6H), 4.6–3.7 (m, 15H). Analysis calculated for $C_{21}H_{22}N_2O_{12}$: C, 51.02; H, 4.49. Found: C, 50.96; H, 4.48.

All other chemicals were reagent grade unless stated otherwise. *p*-Dioxane was purified by the recommended method [14]. Demineralized water was prepared by passing distilled water through three Barnstead D8992 combination cartridges in series. A 10% aqueous solution of tetramethylammonium hydroxide (TMAH) was standardized against potassium hydrogen phthalate and used to prepare a 0.10 M solution of TMAH in 70% dioxane–water (by volume).

Ionization constant determination

The titration procedure for determination of ionization constants was essentially that of Albert and Serjeant [15]. A 0.01 M reagent solution was titrated in the absence of inert salt. Measurements of pH were made with a Fisher Accumet pH meter which could be read to 0.001 pH units. The pH meter was standardized against phthalate and borate buffers both before and after each titration.

Into a thermostated (25.0 or 35.0 ± 0.1°C) titration vessel equipped with a magnetic stirring bar, a glass combination electrode, and a microburet of 5.0 ml capacity, 0.50 mmol of the carboxylic acid in 47.5 ml of 70% dioxane–water (by volume) was introduced. This initial volume was taken to allow for the change in total volume of the solution on titrant addition [15]. For practical purposes, the error caused by volume correction is almost negligible (less than 0.01 pH unit for the central five readings of titration set) with a maximum error of 0.018 pH unit [16]. After 10 min, the titration was initiated by addition of a 0.50 ml aliquot of 0.10 M TMAH and recording the highest stable pH value. Further titrant additions were made in the same fashion. Titrations were conducted in duplicate and values were reproducible within ±0.01 pH unit.

The relationship of Van Uitert and Haas [17] was utilized to evaluate the hydrogen ion concentration from the pH meter value (B).

$$-\log[\mathrm{H}^+] = B + \log U_\mathrm{H}^0 + \log \gamma^{\pm} \qquad (1)$$

Values of the correction factor, $\log U_\mathrm{H}^0$, have been determined experimentally [18] and mean activity coefficients, $\gamma^{\pm}$, were calculated by interpolation from the data of Harned and Owen [19] assuming that the mean activity coefficients are the same on both molal and molar scales.

Ionization of a carboxylic acid (HA) in an aqueous medium gives hydrogen ion (H^+) and the carboxylate anion (A^-). The equilibrium constant is given by eqn. (2)

$$^{\mathrm{T}}K_\mathrm{a}(\mathrm{aq}) = ([\mathrm{H}^+][\mathrm{A}^-]/[\mathrm{HA}])\,(\gamma_{\mathrm{H}^+}\gamma_{\mathrm{A}^-}/\gamma_{\mathrm{HA}}) \qquad (2)$$

which is readily transformed into eqn. (3)

$$^{\mathrm{T}}\mathrm{p}K_\mathrm{a}(\mathrm{aq}) = -\log[\mathrm{H}^+] + \log([\mathrm{HA}]/[\mathrm{A}^-]) + 2\log 1/\gamma^{\pm} \qquad (3)$$

Assuming that γ_{HA}, the mean activity coefficient of the un-ionized acid is unity, the final equation for computing $^{\mathrm{T}}\mathrm{p}K_\mathrm{a}$ in the dioxane–water mixture is obtained by combination of eqns. (1 and 3)

$$^{\mathrm{T}}\mathrm{p}K_\mathrm{a} = B + \log U_\mathrm{H}^0 + \log([\mathrm{HA}]/[\mathrm{A}^-]) + \log 1/\gamma^{\pm} \qquad (4)$$

The thermodynamic functions (ΔG^0, ΔH^0, ΔS^0) associated with the ionization were calculated employing the following standard equations.

$$\Delta G^0\ (25\,^\circ\mathrm{C}) = 1.3646\ {}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}\ (25\,^\circ\mathrm{C}) \quad (\mathrm{kcal}) \tag{5}$$

$$\Delta G^0\ (35\,^\circ\mathrm{C}) = 1.4103\ {}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}\ (35\,^\circ\mathrm{C}) \quad (\mathrm{kcal}) \tag{6}$$

$$\Delta H^0 = 42.06\ [{}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}\ (25\,^\circ\mathrm{C}) - {}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}\ (35\,^\circ\mathrm{C})] \quad (\mathrm{kcal}) \tag{7}$$

$$-\Delta S^0\ (25\,^\circ\mathrm{C}) = 3.353\ [\Delta G^0\ (25\,^\circ\mathrm{C}) - \Delta H^0] \quad (\mathrm{cal}) \tag{8}$$

$$-\Delta S^0\ (35\,^\circ\mathrm{C}) = 3.2446\ [\Delta G^0\ (35\,^\circ\mathrm{C}) - \Delta H^0] \quad (\mathrm{cal}) \tag{9}$$

RESULTS

Thermodynamic ionization constants, ${}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}$, for crown ether carboxylic acids **I**–**IX** in 70% dioxane–water (by volume) at 25 and 35 °C are summarized in Table 1. In addition, ${}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}$ values for two model compounds, acetic and methoxyacetic acids, are also presented. Titration of perchloric acid in the presence and absence of ligand **III** proved that formation of HAH^+ species was negligible.

Within experimental error, the ${}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}$ values for crown ether carboxylic acids **I**–**III** and **IX** were the same at both temperatures. On the other hand, the ${}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}$ values for **IV** and **VI** were slightly larger at the higher temperature; but that for **VIII** was substantially lower at 35 °C. Insufficient amounts

TABLE 1

Thermodynamic ionization constants, ${}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}$, for crown ether carboxylic acids and model compounds in 70% dioxane–water (by volume)

Acid	${}^{\mathrm{T}}\mathrm{p}K_\mathrm{a}$ [a]	
	25.0 °C	35.0 °C
CH_3CO_2H	8.32 [b]	ND [c]
$CH_3OCH_2CO_2H$	7.20 ± 0.02	7.72 ± 0.02
I	7.84 ± 0.04	7.87 ± 0.04
II	7.80 ± 0.04	7.83 ± 0.04
III	7.98 ± 0.02	8.01 ± 0.05
IV	8.45 ± 0.05	8.57 ± 0.05
V	8.42 ± 0.04	ND [c]
VI	8.53 ± 0.02	8.60 ± 0.02
VII	8.71 ± 0.04	ND [c]
VIII	8.34 ± 0.05	8.07 ± 0.04
IX	7.73 ± 0.05	7.72 ± 0.05

[a] Obtained using a set of at least seven determinations.

[b] Ref. 21.

[c] Not determined.

TABLE 2

Thermodynamic parameters for ionization of crown ether carboxylic acids in 70% dioxane–water (by volume)

Acid	Thermodynamic function				
	ΔG^0 (kcal mol^{-1})		ΔH^0 (kcal mol^{-1})	$-\Delta S^0$ (cal mol^{-1} K^{-1})	
	25°C	35°C		25°C	35°C
$CH_3OCH_2CO_2H$	9.8	10.9	−21.9	106	106
I	10.7	11.1	−1.3	40	40
II	10.6	11.0	−1.3	40	40
III	10.9	11.3	−1.3	41	41
IV	11.5	12.1	−5.0	56	56
VI	11.6	12.1	−2.9	49	49
VIII	11.4	11.4	11.4	0	0
IX	10.6	10.9	0.4	34	34

of **V** and **VII** were available to conduct the $^{T}pK_a$ determinations at the higher temperature. Thermodynamic functions, ΔG^0, ΔH^0 and ΔS^0, associated with the ionization of crown ether carboxylic acids **I–IV**, **VI**, **VIII**, **IX** and methoxyacetic acid are recorded in Table 2.

DISCUSSION

The crown ether carboxylic acids **I–IX** provide systematic variation of several structural features. For compounds **I–III** and **VIII**, the crown ether ring size is changed from 13-crown-4 to 14-crown-4 to 16-crown-5 to 19-crown-6 (variation of Y) while the R_1 substituent and pendant acid group remain unaltered. In **III–V**, a common 16-crown-5 ring size and R_1 group are maintained while the pendant acid group is changed. For **III**, **VI** and **VII**, the 16-crown-5 ring size and pendant acid group are held constant but the lipophilicity is markedly changed by replacement of a hydrogen substituent at R_1 with a linear alkyl group. Finally, **III** and **IX** are identical except for the presence of electron-withdrawing nitro groups on both benzene rings in the latter.

Influence of structural variation upon $^{T}pK_a$

The acidity of crown ether carboxylic acid **I** lies between that of acetic acid and methoxyacetic acids. Replacement of two methoxyl group hydrogens of the latter with carbon atoms would be expected to diminish the electron-attracting ability of the alkoxyl group and produce a lower acidity in the crown ether carboxylic acid, as observed.

For compounds **I–III** and **VIII** in which R_1 and R_2 are held constant but the ring size is systematically increased, the minor ring size expansion from

13-crown-4 (in **I**) to 14-crown-4 (in **II**) produces no change in acidity. However, there is a significant decrease in acidity when the ring size is increased to 16-crown-5 (in **III**) and an even more substantial acidity diminution is noted when the ring size becomes 19-crown-6 (in **VIII**). Newcomb and Cram [20] observed that crown ether carboxylic acids in which the acid group points into the polyether cavity are less acidic than closely-related analogs which do not possess a macrocyclic ring. This has been attributed to: (1) transannular hydrogen bonding of the carboxyl group to the crown ether oxygens, and (2) steric inhibition to solvation of the crown ether carboxylate anion. Since steric inhibition to solvation of carboxylate groups in ionized forms of **I**–**III** and **VIII** seems unlikely, the former factor appears to be dominant for these compounds. We propose that hydrogen bonding of the carboxylic groups in **III** and even more so in **VIII** with a transannular dialkyl ether oxygen produces the diminished acidiy. Examination of Corey–Pauling–Kortun (CPK) space-filling models reveals that such association is possible for **III** and even more favorable for **VIII**.

For crown ether carboxylic acids **III**–**V**, the ring size and R_1 substituent are a constant 16-crown-5 and H, respectively, while the pendant group is modified. Compared with **III**, the sidearm length is increased by three methylene groups in **V**. This lengthening of the sidearm produces a substantial decrease in acidity. The CPK models reveal that hydrogen bonding of the carboxyl group in **V** with its transannular dialkyl oxygen should be considerably more efficient than in **III** due to the longer sidearm. The acidity decrease for **IV** compared with **III** undoubtedly arises from replacement of an alpha-hydrogen on the latter with an acid-weakening alkyl group.

In the crown ether carboxylic acid series of **III**, **VI** and **VII**, a constant 16-crown-5 ring size and pendant ionizable group, R_2, are maintained; but R_1 is varied from H to *n*-decyl to *n*-tetradecyl, respectively. Since the introduction of an alkyl group at a site so distant from the carboxylic acid function should exert a negligible inductive effect, the decrease in acidity for **VI** and **VIII** compared with **III** must involve a different interaction. The CPK models show that when the lipophilic alkyl groups in **VI** and **VIII** extend away from the hydrophilic polyether ring, the ionizable group is constrained to the region directly over the crown ether cavity. This should enhance the transannular hydrogen bonding of **VI** and **VII** compared with **III** and produce the observed diminution in acidity.

The final comparison involves compounds **III** and **IX** which differ only in the presence of a nitro group on each benzene ring of the latter. Although strongly electron withdrawing, the two nitro groups are located too far distant from the carboxyl function to exert more than a minor acid-strengthening effect.

Thermodynamic functions for ionization

The ${}^{T}pK_a$ values were determined with a precision of ±0.02 to ±0.05 which would produce an uncertainty of ±0.03 to ±0.07 kcal mol^{-1} in ΔG^0. The temperature variation method utilized here for the computation of ΔH^0 is subject to some error because: (i) the enthalpy change associated with acid ionization is relatively small; and, (ii) values of ${}^{T}pK_a$ have not been obtained at several temperatures which would make possible the use of a more accurate graphical method. Errors of 0.01 in the ${}^{T}pK_a$ determinations at the two temperatures utilized in this study could produce a maximal error of 0.42 kcal mol^{-1} in ΔH^0.

Although the present temperature variation method affords ΔH^0 values which contain relatively large errors, the thermodynamic functions thus calculated (Table 2) are still of considerable utility. Thus the proton ionization of crown ether carboxylic acids **I–IV** and **VI** in 70% dioxane–water is exothermic. On the other hand, the ionization of **VIII** is clearly endothermic. The fairly large negative values of ΔS^0 which are noted for all compounds except **VIII** may be rationalized as arising from requisite additional solvation of the carboxylate anion by water molecules.

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