Crown Ether Acetals: Detection of Cation Binding by Kinetic Measurements

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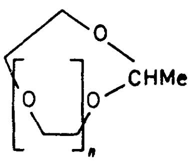
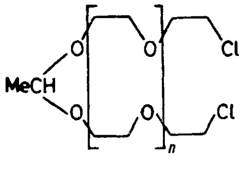
Summary The rates of acid-catalysed hydrolyses of some new macrocyclic ether acetals, analogous in structure to crown ethers, are found to be markedly depressed by some metal ions; the behaviour is consistent with selective cation-binding and a resulting lowering of the basicity of the acetal oxygen atoms.

Compounds related to crown ethers in which one (or more) of the $-OCH_2CH_2O-$ groupings of the ring is replaced by $-OCHRO-$ ('crown ether acetals') are expected to exhibit cation-binding properties similar to those of crown ethers.[1] The only published indication of such behaviour is due to Pedersen himself, who detected weak binding of potassium and caesium ions in one compound (out of three actually prepared and tested).[2] There have been about a dozen scattered reports and patents of syntheses of individual small-ring ether acetals.[3,4] However, apart from work on the n.m.r. spectrum of 1,3,6-trioxacyclo-octane,[5] cyclic ether acetals have not up till now received much attention.

Like other acetals,[6] these compounds undergo acid-catalysed hydrolysis, and we now report a systematic study of this reaction for the series (**1**) (n = 0—5).



(1)



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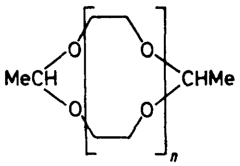

(3)

The stability of the compounds (**1**) with respect to acid-catalysed hydrolysis in dioxan–water (60:40 by volume) at 25 °C shows a minimum for n = 3 (fourteen-membered ring with five oxygens, named† by analogy with Pedersen's

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† Systematic name: 2-methyl-1,3,6,9,12-pentaoxacyclotetradecane.

terminology,[1] 2-methyl-14-crown-5), as indicated by the following second-order rate constants for catalysis by hydrochloric acid:

n	0	1	2	3	4	5
10^3k_2/dm^3 mol^{-1} s^{-1}	2·4	85	159	328	162	120

The effect of alkali metal cations on this hydrolysis rate is shown by the values of k_2^0/k_2^M, where k_2^M is the second-order rate constant for catalysis by hydrochloric acid in the presence of 0·25M-alkali metal (M) chloride, and k_2^0 the corresponding second-order rate constant in the absence of the salt, all rate data referring to the same conditions as before (Table).

Table. Alkali metal ion effects (k_2^0/k_2^M) on acid-catalysed hydrolysis of crown ether acetals (**1**)

n	Li^+	Na^+	K^+	Rb^+	Cs^+
0	0·79	0·79	0·81	0·93	0·90
1	0·61	0·63	0·60	0·68	0·68
2	0·64	0·65	0·63	0·74	0·70
3	0·79	0·85	0·92	1·00	0·91
4	0·68	4·3	4·0	2·6	1·56
5	0·74	1·16	7·7	11	5·6

There is no simple pattern or otherwise remarkable effect in the results given in the first three rows. By contrast, large (up to eleven-fold) rate reductions are displayed in the final two rows, corresponding to acetals containing 17- and 20-membered rings and 6 or 7 oxygen atoms in the ring, respectively. These acetals, 2-methyl-17-crown-6 and 2-methyl-20-crown-7, have very similar ring sizes to 18-crown-6 and related crown ethers and are accordingly expected to exhibit a comparable capacity for cation binding. The salt effects (Table) are therefore taken to show that cation binding reduces the rate of hydrolysis. This is consistent with the assumption that the basicity of the acetal oxygen atoms (the protonation of one of which occurs in the first step of acetal hydrolysis)[6] is lowered by the complexed metal ion. The alternative possible consequence of cation-binding, that the complexed metal ion might itself function catalytically in place of the hydrogen ion and thus lead to a rate enhancement, can now be ruled out. From preliminary studies on the dependence of rates on salt concentration it appears probable that the reactivity of complexed acetal is in fact very much smaller than that of free acetal, so that the relative values of rate constants in the final two rows can be taken as an indication of relative stability constants of the complexes. On this basis, the equilibrium constants for the binding of alkali metal ions by 2-methyl-17-crown-6 (in competition with dioxan-water) are in the sequence $Na^+ \sim K^+ > Rb^+ > Cs^+ \gg Li^+$ whereas the approximate order for 2-methyl-20-crown-7 is $Rb^+ > K^+ > Cs^+ \gg Na^+ \gg Li^+$. Corresponding experiments with chlorides of Group 2A metals gave in both these cases the sequence $Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$, with 2-methyl-20-crown-7 appearing to be particularly selective towards barium. Both these crown ether acetals also showed some binding of ammonium ions. All the results are in qualitative agreement with the ring-size cation size correlation of binding effects.[1]

In contrast to these salt effects, the hydrolysis rates of acyclic ether acetals (**2**) containing 2—6 oxygen atoms were in no way unusual in the presence of the same metal chlorides.

Preliminary experiments were carried out in collaboration with Dr. Th. Bluhm on the n.m.r. spectra of the cyclic ether acetals in the presence of Zeise's salt $[KPtCl_3(C_2H_4).H_2O]$ in deuteriated chloroform as solvent, by the procedure due to Reinhoudt *et al.*[7] In this solvent, 2-methyl-14-crown-5, 2-methyl-17-crown-6, and 2-methyl-20-crown-7 all formed 1:1-complexes, with association constants of 10^5—10^6 mol^{-1} dm^3. Complexing also occurred for the smaller rings, with indications that the ratios ether acetal: cation were greater than unity. Conversely, for the crown ether acetals of even larger ring size (*e.g.* **3**, $n = 4$; 2,16-dimethyl-28-crown-10‡), binding of two potassium ions per crown ether was characterised.

Compounds of the series (**1**) (n = 2—5) and (**3**) (n = 2—6) are new, and were prepared by a modification of a general method for the synthesis of cyclic acetals.[4] The compounds were satisfactorily characterised by combustion analysis, by the amount of acetaldehyde released upon hydrolysis, n.m.r. spectroscopy, and by molecular weight determinations by chemical ionisation mass spectra and by vapour pressure osmometry. Yields and m.p.s. or b.p.s. points (pressure/mm Hg) were as follows: (**1**) n = 1: 29%, 32 °C (1·0); n = 2: 5%, 60 °C (0·20); n = 3: 8%, 82 °C (0·15); n=4: 13%, 120 °C (0·10); n = 5: 20%, 150 °C (0·05); (**3**) n = 2: 1·5%, 36—37 °C; n = 3: 4%, 61—62 °C; n = 4: 1%, 33—34 °C; n = 5: 1%, 52—53·5 °C. Compounds (**2**) (n = 1,2) were synthesised [61% yield, b.p. 126 °C (0·10 mmHg) and 36% yield, 162 °C (0·05 mmHg)] by condensation of acetaldehyde with 2-(2-chloroethoxy)ethanol and with 2-[2-(2-chloroethoxy)ethoxy]ethanol, respectively. Satisfactory analyses were obtained.

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‡ Systematic name: 2,16-dimethyl-1,3,6,9,12,15,17,20,23,26-decaoxacyclo-octacosane.

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