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THE SYNTHESES AND COMPLEXING PROPERTIES OF OXO-12-CROWN-3 AND OXO-18-CROWN-5

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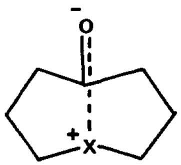
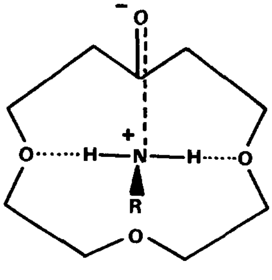
Derivatives of 12-crown-4 and 18-crown-6 in which one of the ethereal oxygens is replaced by a CO group have been synthesised and their complexing abilities towards both metal and organic cations have been assessed. Variable temperature ^1H *decoupled* ^{13}C *n.m.r. spectroscopy reveals the presence of anisometric species in solution when a 1:1 complex is formed between oxo-18-crown-5 and* $(S)\text{-}PhCHMeNH_3{}^+ClO_4{}^-$.

Derivatives of crown ethers incorporating carbonyl groups are of importance for a number of obvious — and not so obvious — reasons. The potential reactivity of these compounds (i) with nucleophiles at their carbonyl carbon atoms and (ii) with electrophiles at either their carbonyl oxygen atoms or at the α-positions to their carbonyl groups renders them much more attractive as synthetic intermediates than the 'ordinary' crown ethers. Our fascination with oxo-crowns was aroused by the speculation[2] that the intramolecular interaction between a carbonyl group and a lone pair of electrons on heteroatoms in medium-sized ring compounds[3], *e.g.* (1) - (3), might find an intermolecular analogy, *e.g.* (4) or (5), in the complexation of neutral primary amines. Inspection of molecular models suggested that the hypothetical complexes (4) and (5) were not too unrealistic goals! For this reason, we undertook the syntheses[4,5] of 6 and 7 — derivatives of 12-crown-4 and 18-crown-6, respectively, in which an oxygen atom is replaced by a carbonyl group and to which, accordingly, we have assigned the trivial names, oxo-12-crown-3 (6) and oxo-18-crown-5 (7) — as a prelude to evaluating their complexing abilities.



1 X = O
2 X = NMe
3 X = S



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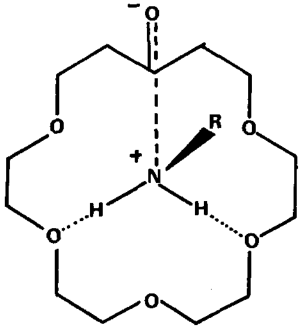

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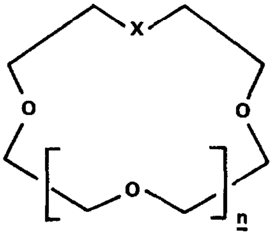
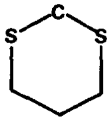
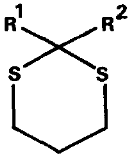


	n	X
6	1	CO
7	3	CO
12	1	
13	3	

	R^1	R^2
8	H	CH_2CH_2OH
9	H	$CH_2CH_2OSiMe_2Bu^t$
10	CH_2CH_2OH	$CH_2CH_2OSiMe_2Bu^t$
11	CH_2CH_2OH	CH_2CH_2OH



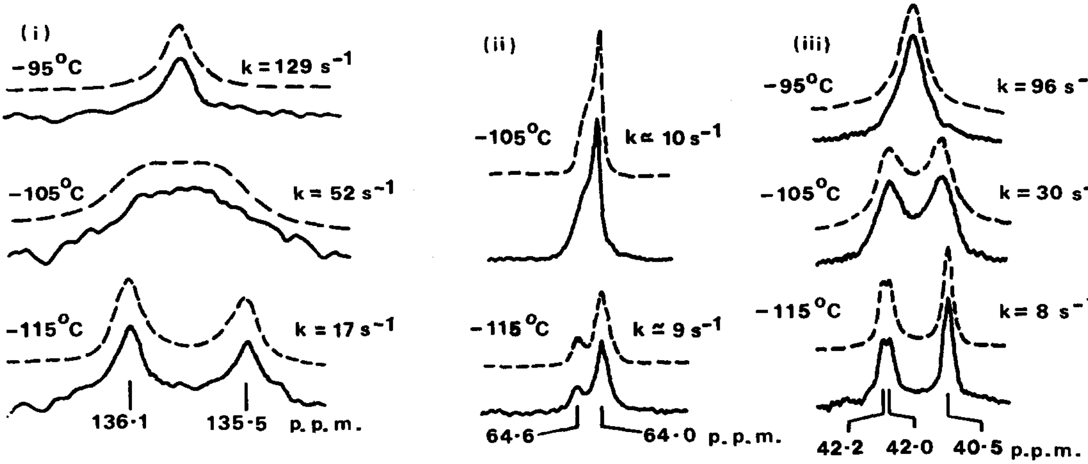


Figure. Observed (full line) and computed (broken line) spectra of (i) the quaternary aromatic carbons, (ii) the β-CH$_2$ carbons, and (iii) the α-CH$_2$ carbons of 7.(*S*)-PhCHMeNH$_3^+$ClO$_4^-$

When 2-(2'-hydroxyethyl)-1,3-dithiane[6] (8) was treated[7] in DMF with an equivalent of Bu^{t}Me$_2$SiCl in the presence of imidazole as base, the mono-t-butyldimethylsilyl ether (9) was isolated[8] after vacuum distillation (b.p. 87-88° at 0.03 mm) in 91% yield. Reaction of 9 with equivalents of Bu^{n}Li and ethylene oxide gave an 89% yield of 10 (b.p. 138-139° at 0.1 mm) from which 2,2-bis-(2'-hydroxyethyl)-1,3-dithiane (11), m.p. 52-53°, was obtained in 60% yield on treatment with Bu$_4^n$ NF in THF (*cf.* ref 7) at 20°C. Condensation (NaH/DMSO) of 11 with diethyleneglycol bistosylate[9] at 70°C gave[10] (24%) the spiro-12-crown-3 derivative (12) as an oil after column chromatography (ether/light petroleum 7/3) on SiO$_2$. Oxidative hydrolysis[11] (HgCl$_2$/CaCO$_3$/MeOH/H$_2$O) of this 1,3-dithiane derivative afforded (87%) oxo-12-crown-3 (6) as an oil after vacuum distillation (b.p. 83-85° at 0.02 mm), ^{1}H n.m.r. data: δ (CD$_2$Cl$_2$) 2.64 (t, *J* = 5.5 Hz, 4H, 2xα-CH$_2$), 3.40-3.60 (m, 8H, 2xOCH$_2$CH$_2$O), and 3.78 (t, *J* = 5.5 Hz, 4H, 2 x β-CH$_2$). Condensation (NaH/THF) of 11 with tetraethyleneglycol bistosylate[9] at 60°C gave (54%) the spiro-18-crown-5 derivative (13) as an oil after column chromatography (EtOAc) on SiO$_2$. Oxidative hydrolysis[11] (HgCl$_2$/CaCO$_3$/MeOH/H$_2$O) of this 1,3-dithiane derivative afforded oxo-18-crown-5 (7), m.p. 36-37°, ^{1}H n.m.r. data: δ (CD$_2$Cl$_2$) 2.69 (t, *J* = 5.5 Hz, 4H, 2xα-CH$_2$), 3.56 and 3.59 (2xs, 16H, 4xOCH$_2$CH$_2$O), and 3.72 (t, *J* = 5.5 Hz, 4H, 2xβ-CH$_2$) in 64% yield after column chromatography (CH$_2$Cl$_2$/EtOH, 19/1) on SiO$_2$.

When a molar equivalent of PhCH$_2$NH$_2$ is added to a CD$_2$Cl$_2$ solution of either (i) oxo-12-crown-3 (6) or (ii) oxo-18-crown-5 (7), no significant changes were observed in the signals for the crown protons in the ^{1}H n.m.r. spectra. These negative results indicate that PhCH$_2$NH$_2$ does not form 1:1 complexes[12] with either 6 or 7 in CD$_2$Cl$_2$. However, both 6 and 7 form 1:1 complexes with RNH$_3^+$ and R$_2$NH$_2^+$ salts[13] in CD$_2$Cl$_2$. In each case, downfield shifts [*ca.* 0.01-

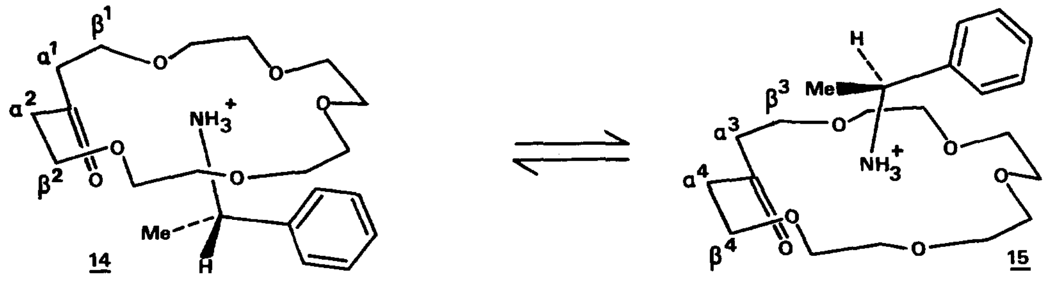


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Table 1. Temperature dependent ^{1}H n.m.r. spectral data[a] and kinetic and thermodynamic parameters for the 1:1 complexes formed between selected $RNH_3^+ClO_4^-$ salts and oxo-18-crown-5 (7).

R	^{1}H N.m.r. probes	(δ at 30°)	T_c, °C[a] ± 3°	Δν (°C)[a] ± 2Hz	k_c[a] s^{-1}	$\Delta G_c^\ddagger$, ±0.3[a] kcal mol^{-1}
Me	Crown α-CH_2	(2.81)	-78	56(-105)	125	9.4
Et	Salt NH_3^+	(6.60)	-92	73(-106)	163	8.6
Pr^i	Crown α-CH_2	(2.83)	-100	42(-106)	92	8.4
	Salt Me	(1.37)	-102	25(-106)	54	8.5
	Salt NH_3^+	(6.45)	-100	47(-106)	103	8.3
Bu^t	Crown α-CH_2	(2.80)	-79	42(-106)	92	9.4
$PhCH_2$	Crown α-CH_2	(2.72)	-88	64(-106)	141	8.8
(S)-PhCHMe	Salt Me	(1.73)	-100	42(-108)	92	8.4

[a] All spectra were recorded in CD_2Cl_2 at 220 MHz on a Perkin Elmer R34 spectrometer with Me_4Si as "lock" and internal standard. Abbreviations used are: T_c, coalescence temperature; Δν, frequency separation of appropriate ^{1}H n.m.r. probe with the temperature at which it was measured indicated in parenthesis; k_c, exchange rate constant at T_c calculated from the expression, $k_c = \pi\Delta\nu/2^{\frac{1}{2}}$; $\Delta G_c^\ddagger$, free energy of activation calculated from the Eyring equation.

0.08 ppm for 6 and *ca.* 0.01-0.14 ppm for 7] were observed in the signals for the crown protons when one molar equivalent of salt was added. Dynamic ^{1}H decoupled ^{13}C n.m.r. spectroscopy[14] at 90.52 MHz on the 1:1 complex formed between 7 and *(S)*-$PhCHMeNH_3^+ClO_4^-$ in CD_2Cl_2 proved to be particularly useful in unravelling the structural behaviour of the complex in solution. Oxo-18-crown-5 (7) exhibits resonances[15] at δ 43.8, 66.5, and 208.7 for the α-CH_2, β-CH_2, and CO carbons respectively. Small upfield shifts of 0.5 and 0.8 ppm respectively for the α- and β-CH_2 carbons and a downfield shift of 1.7 ppm for the CO carbon were observed, together with 'extra' signals for the carbons in the *(S)*-$PhCHMeNH_3^+$ ion, when the 1:1 complex was formed. On cooling the solution down to -115°C, the signal for the CO carbon, as well as those for three of the four aromatic carbons, separated out into two equal intensity signals in each case. The temperature dependent behaviour of the signal for the quaternary aromatic carbon is illustrated in the Figure, along with the more complicated spectral changes in the signals for the α- and β-CH_2 carbons obtained on lowering the temperature of the CD_2Cl_2 solution. This pattern of spectral events is consistent[16] with equilibration occurring between equally populated anisometric[17] complexes in which the CO oxygens are *syn* (14) and *anti* (15) to the *(S)*-PhCHMe group. Under conditions of slow interconversion on the ^{13}C n.m.r. time scale between 14 and 15, a maximum of eight resonances arising from carbon atoms labelled α^1, α^2, α^3, α^4, β^1, β^2, β^3, and β^4 are possible for the α- and β-CH_2 carbons. At -115°C, three signals with relative intensities of 1:1:2 were observed for the α-CH_2 carbons and two signals with relative intensities of 1:3 were observed for the β-CH_2 carbons. Line shape analysis of these signals,as well as those for the quaternary aromatic carbons, gave excellent agreement in the value (8.4 kcal mol^{-1}) obtained for the free energy of activation associated with the interconversion, $14 \rightleftharpoons 15$. Also, this value corresponds exactly to the $\Delta G_c^\ddagger$ value (see Table 1) obtained from an approximate analysis of the temperature dependent ^{1}H n.m.r. spectra. This observation leads us to believe that the $\Delta G_c^\ddagger$ values for the other 1:1 complexes in Table 1 have their origins in barriers involving complex dissociations leading to interconversions analogous to $14 \rightleftharpoons 15$. Dynamic ^{1}H n.m.r. spectroscopy was not useful in providing quantitative data for 1:1 complexes formed between (i) oxo-18-crown-5 (7) and $R_2NH_2^+$ salts and (ii) oxo-12-crown-3 (6)

Table 2. The association constants ($K_a \times 10^{-6}$, M^{-1})^a for the formation of 1:1 complexes between oxo-12-crown-3 (6), oxo-18-crown-5 (7), and 18-crown-6 and some selected picrate salts in $CDCl_3$ at 25°C.

Crown/Cation	Li^+	Na^+	K^+	Rb^+	NH_4^+	$MeNH_3^+$	$Bu^tNH_3^+$
Oxo-12-crown-3 (6)	0.005	0.016	0.0004	0.003	0.004	0.005	0.0006
Oxo-18-crown-5 (7)	0.033	0.066	2.11	0.56	0.83	0.027	0.003
18-Crown-6	0.43	1.3	>100000	37000	2420	32.5	3.31

[a] The K_a values (corrected for the solubilities of the crowns in the aqueous phases) were determined by a u.v. spectroscopic method following extraction of aqueous picrate solutions with $CDCl_3$ solutions of the crowns (*cf*. S.S. Moore, T.L. Tarnowski, M. Newcomb, and D.J. Cram, *J. Amer. Chem. Soc.*, **99**, 6398 (1977)).

and either RNH_3^+ or $R_2NH_2^+$ salts. We conclude that these complexes are very much weaker and that the free energy of activation for any process involving dissociation of the cation from the crowns is < 8.0 kcal mol^{-1}. Moreover, the association constants for 1:1 complex formation in $CDCl_3$ involving picrate salts listed in Table 2 show that the orders of stabilities are 18-crown-6 > oxo-18-crown-5 (7) > oxo-12-crown-3 (6) for all cations. The selectivities of 18-crown-6 and oxo-18-crown-6 (7) are similar but both differ slightly from that exhibited by oxo-12-crown-3 (6).

References and Footnotes

1. Address all correspondence to this author at the Corporate Laboratory, Imperial Chemical Industries Ltd., P.O. Box No. 11, The Heath, Runcorn, Cheshire WA7 4QE.
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10. A second component was isolated in 11% yield. It was characterised as the dimeric dispiro-24-crown-6 derivative of 12 and yielded the corresponding dioxo-24-crown-6, b.p. 185-187° at 0.02 mm, on oxidative hydrolysis.
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12. Nonetheless, it was possible (*cf*. R.F. Borch, M.D. Bernstein, and H.D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971)) to effect reductive amination of 7 with $PhCH_2NH_2$ in methanol in the presence of $NaBH_3CN$ at *ca*. pH 6 to afford the appropriate secondary amine.
13. This observation for 7 is in contrast with that recorded (R.M. Izatt, N.E. Izatt, B.E. Rossiter, J.J. Christensen, and B.L. Haymore, *Science*, **199**, 994 (1978) for 18-crown-6, which forms extremely weak complexes with $R_2NH_2^+$ salts.
14. We thank Dr. W.E. Hull of Bruker for carrying out this experiment for us on a WH-360 spectrometer.
15. There are additional resonances at δ 70.7, 70.8 and 71.0 for the OCH_2CH_2O carbons.
16. Examination of C.P.K. space-filling molecular models shows that, although the CO oxygen can pass through the 18-membered ring in the free crown, it cannot in the complex.
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