Lipophilic Cage Compounds from 1,7-Dioxa-4,10-diazacyclododecane: Exceptionally Strong Ligands for the Sodium Cation and Effective Anion Activators in Non-polar Media

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Lipophilic cage compounds (**1**) and (**2**) containing two diaza-crown units (**3**) form very stable complexes with sodium salts; they allow effective activation of hydrophilic and/or highly electronegative anions in non-polar media.

Anions are strongly activated in non-polar solvents by bulky quaternary onium cations, or lipophilic multidentate macrocyclic ligands capable of complexing inorganic cations.[1] With large and/or polarizable anions any of these systems can be used. However, with hydrophilic and/or highly electronegative anions, the lack of chemical stability of quaternary salts,[2] and the very poor complexation constants of multidentate ligands[3,4] (especially crown ethers)[3b] make all these systems scarcely effective for anion activation.

Here we report the synthesis and the unique behaviour of cage compounds (**1**) and (**2**), derived from 1,7-dioxa-4,10-diazacyclododecane (**3**). The benzyl-tosyl-diaza-crown (**4**)[5] was treated with ethyl chloroformate in anhydrous tetrahydrofuran (THF) (60 °C, 1 h) to give a 90% yield of the glassy ethoxycarbonyl derivative (**5**). Hydrolysis with NaOH in ethanol (reflux, 3 days) afforded an 80% yield of the tosyl-diaza-crown (**6**) (m.p. 105—107 °C). Reaction of (**6**) with the bis(toluene-*p*-sulphonate) (**7**) or (**8**) and solid Na_2CO_3 in refluxing acetonitrile (3 days) gave 72% of (**9**) (m.p. 112—113 °C) or 78% of (**10**) (m.p. 131—133 °C), respectively, which were treated with $LiAlH_4$ in THF (reflux, 60 h) to give almost quantitative yields of (**11**) or (**12**) (oils).

The template effect of the sodium cation was essential in the last step. The cage compounds (**1**) or (**2**) were obtained in 60—70% yields when acetonitrile solutions of (**11**) or (**12**) were refluxed for 48 h with ethylene bis(toluene-*p*-sulphonate) in the presence of solid Na_2CO_3. Other cations (*e.g.* Li^+ and Ag^+) were ineffective.†‡

The waxy sodium toluene-*p*-sulphonate complexes (**1a**) and (**2a**) were easily converted into the crystalline perchlorates (**1b**) (m.p. 177—179 °C) and (**2b**) (m.p. 241—244 °C). The latter, dissolved in methanol and treated with the potassium salts of various anions, quantitatively afforded the corresponding salts (**1c**—**f**) and (**2c**—**f**), owing to the insolubility of $KClO_4$.§

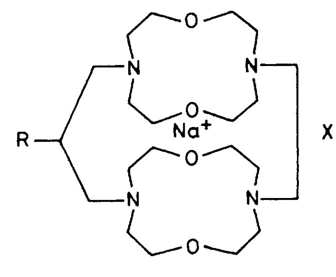
An unusual feature of the complexes (**1**) and (**2**) is their exceptionally high stability. Thus the sodium cation remains complexed after refluxing (**1**) or (**2**) for 3 h in aqueous 6 M-HCl, in contrast to cryptates which are immediately decomplexed in acidic media.[6]

Complexes (**1**) and (**2**) can be used as anion activators both in stoicheiometric and catalytic reactions. Anionic activation is comparable with that observed[4b] with lipophilic $[K^+ \subset (2.2.2,C_{14})]X^-$ cryptates. Representative results of nucleophilic substitutions carried out in anhydrous chlorobenzene [equation (1)] are reported in Table 1.

$$\text{n-}C_8H_{17}OSO_2Me + (Na^+ \subset \text{ligand})X^- \xrightarrow{\text{PhCl, 60 °C}} \text{n-}C_8H_{17}X + (Na^+ \subset \text{ligand})MeSO_3^- \quad (1)$$

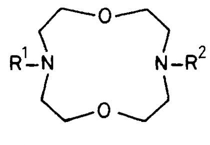
Complexes like (**1e,f**) and (**2e,f**) are particularly useful catalysts for liquid–liquid phase-transfer reactions carried out in the presence of strongly hydrophilic and/or highly electronegative anions. Indeed, such reactions are totally inhibited by traces of lipophilic anions, such as ClO_4^-, I^-, *etc.*[7] The high stability of the complexes ensures a high catalytic efficiency. For example, n-octyl methanesulphonate was converted into the corresponding fluoride in 75% yield by heating for 1 h at 110 °C, in the presence of saturated aqueous KF (10 mol. equiv.) and 0.1 mol. equiv. of (**2e**) or (**2f**). Diphenylmethane was 50% deuteriated by stirring with 15 M-NaOD–D_2O and 0.2 mol. equiv. of (**2f**) for 5 h at 70 °C, under argon. Benzophenone was the product (95% yield in 1 h) when the same reaction was carried out with NaOH–H_2O under an oxygen atmosphere.

Quaternary ammonium salts have also been used for this kind of reaction,[7—9] but they are rapidly decomposed.[2] An important difference is that cage compounds (**1**) and (**2**) are

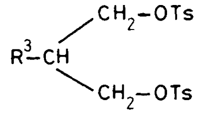


(**1**) R = $C_{16}H_{33}$-n (**2**) R = CH_2Ph

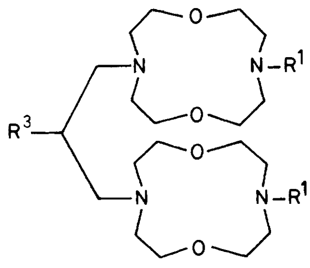
a; X = OTs
b; X = ClO_4
c; X = I
d; X = Cl
e; X = F
f; X = OMe



(**3**) $R^1 = R^2 = H$
(**4**) R^1 = Ts, $R^2 = CH_2Ph$
(**5**) R^1 = Ts, $R^2 = CO_2Et$
(**6**) R^1 = Ts, R^2 = H



(**7**) $R^3 = C_{16}H_{33}$-n
(**8**) $R^3 = CH_2Ph$



(**9**) R^1 = Ts, $R^3 = C_{16}H_{33}$-n
(**10**) R^1 = Ts, $R^3 = CH_2Ph$
(**11**) R^1 = H, $R^3 = C_{16}H_{33}$-n
(**12**) R^1 = H, $R^3 = CH_2Ph$

Ts = *p*-$MeC_6H_4SO_2$

Table 1. Second-order rate constants in nucleophilic substitutions promoted by polycyclic ligands.[a]

	$k \times 10^2$/dm³ mol⁻¹ s⁻¹		
X^-	(**1**)	(**2**)	$[K^+ \subset (2.2.2,C_{14})]X^-$ [b]
I^-	0.90	0.86	0.87
Cl^-	2.3	3.2	5.1

[a] At 60 °C; 40 cm³ of a 1.07×10^{-2} M chlorobenzene solution of complexed ligand and 10 cm³ of a 0.1 M chlorobenzene solution of n-$C_8H_{17}OSO_2Me$. [b] From ref. 4b.

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† The lithium-templated synthesis of bis(1,7-dioxa-4,10-diazacyclododecane) doubly bridged with ethylene chains has been described by Dale.[5] This compound too forms stable complexes with sodium salts.

‡ As pointed out by a referee, an alternative synthetic route to (**1**) and (**2**) could be envisaged involving the insertion first of the ethylene bridge following the already described procedure,[5] and then of the 3-carbon-atom bridge. The two approaches are substantially equivalent, but we met difficulties in obtaining the mono-ethylene bridged intermediate in acceptable yields, whereas our synthesis has the advantage of good lipophilicity, and therefore of easy purification, of the mono-bridged intermediates (**9**)—(**12**).

§ All the compounds gave analytical and spectral data in agreement with the proposed structures.

much more chemically stable than quaternary salts, and can be easily recovered at the end of reaction.

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