Rearrangement of 1,3-Bis(azacrown)-2-chloropropanes:† the Effect of Alkali Metal Ion on Neighbouring Group Participation

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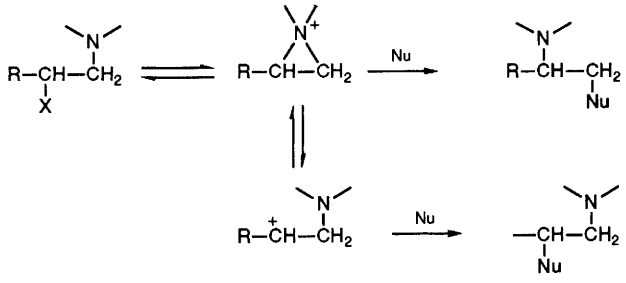
A pronounced effect of alkali metal ion on rate and product distribution has been found in the reaction of the twelve-, fifteen- and eighteen-membered 1,3-bis(azacrown)-2-chloropropanes **1a–c** with benzyl oxide–benzyl alcohol base–solvent system.

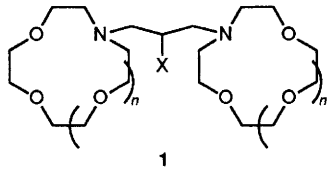
Neighbouring group participation[1,2] is responsible for the unusual reactivity of β-halogenoamines. When a tertiary amino group is involved[3–5] in the participation, an aziridinium salt[6–8] is the primary product which undergoes rapid ring opening upon nucleophilic attack (Scheme 1). Thus, the β-halogenoamines behave as powerful alkylating agents. Their biological properties (cytotoxic, mutagenic, cancerostatic *etc.*) have attracted considerable attention.[9]

β-Halogen substituted derivatives of azacrowns attracted our interest in this context. Monoazacrown compounds can form firm complexes with alkali metal ions[10,11]. When a β-halogenalkyl group is attached to the pivotal nitrogen atom, introduction of the metal ion into the macroring cavity might influence the reactivity of the halogenamino grouping. Since the site of action of many cytotoxic agents is intracellular, metal ion complexation might influence also transport across the cell membrane as well as selective interaction with the cellular target.



Scheme 1

† Azacrown = Polyoxamonoazacycloalkan-*N*-yl.



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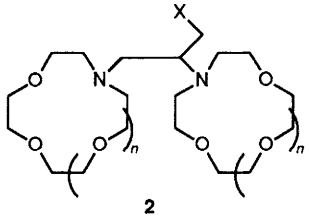

2

1

a; X = Cl, n = 1
b; X = Cl, n = 2
c; X = Cl, n = 3
d; X = OH, n = 1
e; X = OH, n = 2
f; X = OH, n = 3
g; X = OCH_2Ph, n = 1
h; X = OCH_2Ph, n = 2
i; X = OCH_2Ph, n = 3

2

a; X = OCH_2Ph, n = 1
b; X = OCH_2Ph, n = 2
c; X = OCH_2Ph, n = 3

Consequently we have investigated the effect of alkali metal ion on the rate of nucleophilic substitution in the homologous series of twelve-, fifteen- and eighteen-membered 1,3-bis-(monoazacrown)-2-chloropropanes **1a–c** in benzyl alcohol in the presence of the conjugate base. The chlorides **1a–c** were prepared from the corresponding 1,3-bis(monoazacrown)-2-hydroxypropanes[12] **1d–f** by reaction with thionyl chloride in chloroform and isolated as bis-perchlorate salts.‡

The perchlorates of the derivatives **1a–c** were allowed to react with an excess of a 0.5 mol dm^{-3} solution of the alkali benzyl oxide (M = Li, Na, K) in benzyl alcohol, each affording two products which were assigned§ the structures of the isomeric benzyloxy-derivatives **1g–i** and **2a–c**, respectively. Product formation was followed by HPLC and found to obey pseudo-first-order kinetics. The observed rates and product distribution are summarized in Table 1.

A very marked effect of metal ion on the overall rates is apparent in the reaction of all the derivatives **1a–c** investigated. For the eighteen-membered ring derivative **1c**, the rates decrease gradually with increasing metal ion diameter in the order $k_1^{(Li)} > k_1^{(Na)} > k_1^{(K)}$, the overall range of rate constants being greater than 10^2. A different pattern of rate variation is found for the twelve- and fifteen-membered ring compounds **1a** and **1b**, with the rate coefficients following the order $k_1^{(Li)} \approx k_1^{(K)} > k_1^{(Na)}$.

In accord with the principle of best fit,[15] the complex stability[9,10] of the eighteen-membered monoazacrowns with alkali metal ions is known to vary in the order Li < Na < K, whereas the order Li ≤ K < Na holds for the corresponding twelve- and fifteen-membered macrorings. An inverse proportionality thus apparently exists between the observed overall displacement rates and the substrate complexation ability. The metal ion–nitrogen lone electron pair interaction controlling the neighbouring group participation in the rate-determining cyclisation step (Scheme 1) is assumed to be the factor responsible.

Table 1 Overall rates and products in the reaction of derivatives **1a–c** with alkali metal benzyl oxides in benzyl alcohol at 24 °C

Substrate	M in $PhCH_2OM$	$k_1 \times 10^6$/ s^{-1}	Product	Ratio
1a	Li	42.1	2a : 1g	3.7 : 1
	Na	5.4	,,	3.5 : 1
	K	48.3	,,	4.6 : 1
1b	Li	50.6	2b : 1h	0.74 : 1
	Na	3.5	,,	1.7 : 1
	K	45.0	,,	2.6 : 1
1c	Li	329.0	2c : 1i	1.9 : 1
	Na	46.4	,,	9.0 : 1
	K	2.3	,,	1.9 : 1

As Table 1 shows, the cation identity also affects product composition in the reaction. However, no correlation can be found between the overall rates and the product distribution suggesting that different factors control the aziridinium ring-forming and the ring-opening step. Two possible mechanisms, S_N2 and S_N1, can be involved in the ring-opening step (Scheme 1) in the reaction, the former preferring nucleophilic attack at the primary[4,5,7,8] carbon atom of the aziridinium salt whereas the latter prefers attack at the secondary[5] atom. The mixture of the unrearranged (**1d–f**) and rearranged (**2a–c**) products obtained in the reaction of the azacrown derivatives **1a–c** may thus be viewed as resulting from S_N1–S_N2 competition; however, no simple explanation for the cation effect can be offered on the basis of the present evidence.

Qualitatively similar rate and product data have been obtained in the analogous reaction of compounds **1a–c** with alkali hydroxides in aqueous solution.

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‡ Satisfactory elemental analyses were obtained for perchlorates of **1a–c**. **1a**·$2HClO_4$, m.p. 238–240 °C (decomp.); **1b**·$2HClO_4$ (monohydrate), m.p. 207–208 °C (decomp.); **1c**·$2HClO_4$ (dihydrate) m.p. 95–97 °C (decomp.).

§ The individual isomeric products were isolated from the reaction mixture by column chromatography on alumina (Reanal, act. II) using $CHCl_3$ as eluent and compared with samples prepared by an unambiguous synthesis.[13,14]

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