

DIAZA-CROWN ETHERS—VI

A MECHANISM FOR METAL ION PROMOTED FORMATION OF MACROCYCLIC DIAZAOLIGOETHERS

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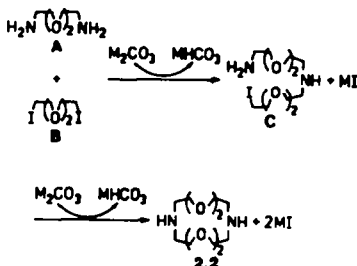
Abstract—The mechanism of the formation of 1,7,10,16-tetraoxa - 4,13 - diazacyclooctadecane has been studied from both a thermodynamic and a kinetic point of view. The cyclisation is favoured by the presence of an alkali metal ion, which forms a complex with the ring precursor. Both this intermediate and the complex react with starting material, but only the complex forms a cyclic product. The rate constants of these reactions have been determined by using simulation methods.

We have recently developed a method for the synthesis of macrocyclic diazaoligo-ethers in the presence of alkali metal ions, without using high dilution techniques.¹ Such reactions, sometimes called "template reactions", have been known for the last decade within the field of crown ether chemistry, and several reviews have appeared.²⁻⁴ The function of the "template" is not fully understood. Some mechanistic investigations concerning the influence of the metal ion of the formation of crown ethers with different ring size have been published.⁵⁻⁷ However, the results are not unambiguous. For some reactions the existence of a "template effect" has been questioned.⁸⁻⁹ Kinetic measurements of the formation of macrocyclic oligoethers have been made, and these indicate participation of the metal ions.¹⁰

We now propose a mechanism for the formation of 1,7,10,16 - tetraoxa - 4,13 - diazacyclooctadecane (2,2) based on the yields with different alkali metal ions present and on the reaction kinetics involved.

RESULTS AND DISCUSSION

The formation of the diaza-crown ether 2,2 can schematically be represented by Scheme 1. The metal



carbonates and hydrogen carbonates are insoluble in the solvents used¹¹ and thus the acid-base reaction is a two phase reaction, which generates the corresponding metal iodide. By-products are, e.g. tri-, tetra- and polymers of A and B. By using different metal carbonates we have found that 2,2 is formed in varying yields (Table 1).

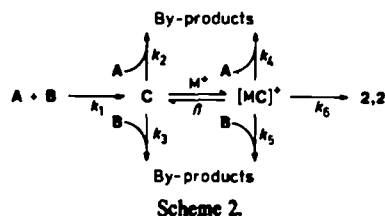
It has been shown that the crown ethers form strong complexes with the alkali ions in acetonitrile.¹² If dicyclohexyl-18-crown-6 is present in excess over metal

Table 1. The yields (%) of 2,2 in some solvents with different alkali metal carbonates.

Solvent	Na ₂ CO ₃	K ₂ CO ₃	Cs ₂ CO ₃
Acetonitrile	44	27 ^a	15
1,2-Dimethoxy ethane	8	24	15
Dioxane	16	24	-
Methanol	-	<5	-

^aThe yield decreased to 4% if dicyclohexyl-18-crown-6 was present in excess over KI formed.

salt formed in the reaction, the possibility for the metal ion to participate in the ring formation is restricted. In this experiment the yield decreased from 27 to 4%, which clearly shows that the metal ion promotes the formation of a cyclic product. It is probable that the acyclic intermediate C forms complexes with the alkali ions since the corresponding complexes with the cyclic 2,2 are strong in acetonitrile.¹³ Due to favourable orientation of C in the complex [MC]⁺ the product 2,2 may be formed. The reaction pathways are illustrated in Scheme 2, where k₁-k₆ represent the rate constants and β the equilibrium constant for complex formation, which can be regarded as a fast process.¹⁴



When the excess of solid potassium carbonate was changed from threefold to twofold, no difference in yield was observed, indicating that the acid-base reactions, as expected, are fast. The direct formation of 2,2 from C has been excluded due to the very low probability of ring formation at the relatively high concentrations used.¹⁵ A continued reaction of 2,2 with B was also excluded. In a separate experiment a mixture of B (0.1 M) and 2,2 (0.1 M) was refluxed in an acetonitrile solution of NaI

Table 2. The solubilities (in mM) of some alkali metal salts in different solvents at b.p.

Solvent	NaI	KI	KOTs	KBPh ₄	CaI
Acetonitrile	>1000	100	3	70	30
1,2-Dimethoxyethane	>3000	3	-	-	2
Dioxane	40	30	-	-	-
Methanol	-	>1000	-	-	-

(0.2 M) over Na₂CO₃(s). No significant change of the starting materials was observed after 3 hr.

The yield of 2, 2 should be dependent on the degree of association of the complex [MC]⁺, which is determined both by the magnitude of the formation constant and the metal ion concentration. When acetonitrile was saturated with MI before the reaction started, the yield did not increase for M=Na or K. Since, at least for M=Na the concentration increased markedly (Table 2), this can only be explained if the formation constant is so high that the association is complete even at low concentrations of M⁺. For M=Cs a slight increase in yield, from 15 to 17%, was observed, which might possibly be due to a smaller formation constant.

The effect of incomplete association is more pronounced in 1,2-dimethoxyethane (Table 1). As Na⁺ is strongly solvated by this glyme,¹⁶ the formation constant should be small. By increasing the concentration of NaI to saturation (Table 2) the yield increased from 8 to 31%. In dioxane, the yields are different, despite the equal solubilities of NaI and KI (Table 1). The low yield with K₂CO₃ in methanol (Table 1) is probably due to weak complex formation, which is substantiated by the low formation constant with 2, 2 (1.1 × 10³ M⁻¹).¹⁷ The best yields are obtained when the interaction between the metal ion and the solvent is weak, which will favour formation of the complex [MC]⁺.

The most common leaving-group used in crown ether syntheses has been *p*-toluenesulfonate (OTs).²⁻⁴ When OTs was used instead of I in acetonitrile with K₂CO₃ as base, the yield was significantly lower (20 vs 27%). The solubility of KOTs is very low, but the K⁺ concentration could be increased by saturating the solution with KBPh₄ (Table 2) and then the yield increased to 25%. This indicates that there is no major mechanistic difference between iodides and tosylates.

Even though there is complete association between the intermediate C and Na⁺ or K⁺ in acetonitrile, the yields

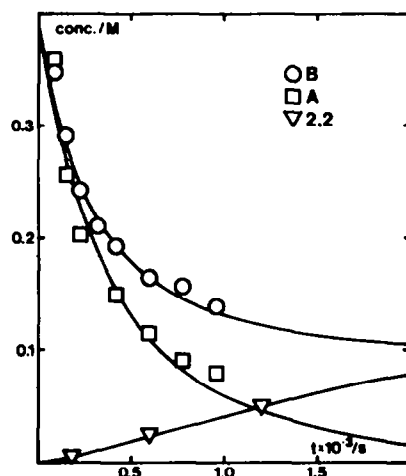


Fig. 1. Computer simulated concentration as time profiles and measured values for the reaction with Na⁺ as promoting ion.

are not higher than 44 and 27%, respectively. This shows that [MC]⁺ reacts to give both by-products and 2, 2 (Scheme 2), and that the rate of cyclisation and/or the rates of the side-reactions are different for the two ions.

The disappearance of A and B and the appearance of 2, 2 was followed by gc. The primary amine A had to be converted to a corresponding imine before analyses, and therefore the accuracy was lower than for B. The changes in concentration were compared with those obtained from computer simulations of the reactions in Scheme 2. The side reactions of C are neglected since there is almost complete association with M⁺ and *k*₂ and *k*₃ should be smaller than *k*₁. Therefore only *k*₁, *k*₄, *k*₅ and *k*₆ are considered. The values of the rate constants which gave the best agreement are given in Table 3. In a separate experiment with A in tenfold excess over B (0.5

Table 3. Rate constants from computer simulations, which agree with experimental results in acetonitrile at its b.p.

Promoting-ion	$\frac{k_1}{M^{-1} s^{-1}}$	$\frac{k_4}{M^{-1} s^{-1}}$	$\frac{k_5}{M^{-1} s^{-1}}$	$\frac{k_6}{s^{-1}}$
Na ⁺	6.7 × 10 ⁻³	4.2 × 10 ⁻³	1.7 × 10 ⁻⁴	3.0 × 10 ⁻⁴
K ⁺	1.2 × 10 ⁻²	5.0 × 10 ⁻³	5.0 × 10 ⁻³	2.5 × 10 ⁻⁴

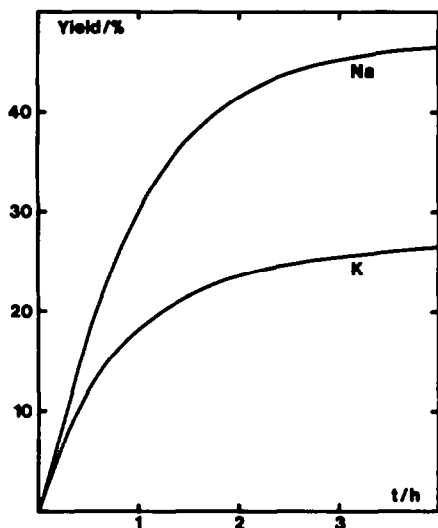


Fig. 2. Computer simulated yield vs time profiles for the formation of 2,2 with Na⁺ or K⁺ as promoting ion.

and 0.05 M), the disappearance of B was followed, and k_1 was found to be $8.6 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$, which is in reasonable agreement with the value for sodium obtained from the simulations. The deviation for potassium might be explained by the different ionic medium. A computer simulation with the rate constants in Table 3, was also used to extrapolate the yield of 2,2. Figure 2 shows that the reactions are almost complete after 3 hr, and the yields are in accordance with those in Table 1.

The function of the promoting ion in the reaction is to form a complex with the ring precursor and thus to increase the probability of ring closure. This complex can also react with the starting material, and the rates of these reactions determine the yield of cyclic product. In acetonitrile the possibility for the complex to react with the iodide B is much less with Na⁺ than K⁺ as promoter, but the rate of cyclisation does not change. However, if the metal ion concentration is low and/or the formation constant is small, some of the intermediate C may not be associated and forms no cyclic product. Thus both kinetic and thermodynamic factors are controlling the mechanism.

EXPERIMENTAL

The solvents, the alkali metal iodides and the carbonates were of analytical grade quality and were used without further

purification. The syntheses of A, B and 2,2 have been described earlier.¹

Glc analyses were performed using a Hewlett-Packard 5830A system with a 1 m 3% OV101 on Chromosorb W column.

Determinations of the yields. B (10 mmol) was added to a boiling soln of A (10 mmol) in 25 ml of solvent over 60 mmol finely ground alkali metal carbonate. The mixture was refluxed for 3 hr and then filtered. The glc analyses were performed on a diluted sample of the filtrate.

Kinetic experiments. A soln of B (4 ml, 10 mmol) was added to a boiling soln of A (21 ml, 10 mmol) over 60 mmol finely ground alkali metal carbonate. In the case of Na the solvent was 0.2 M NaI in acetonitrile, and for K pure acetonitrile. Samples (0.05 ml each) were taken from the mixture and added to 0.5 ml of 2-butanone over 3 Å molecular sieves thus terminating the reaction (the primary amines and the ketone rapidly form imines). In the analyses, which were performed by glc, the amine was detected as the corresponding imine with 2-butanone. The internal standard used in the analyses was present during the reaction.

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