

Macrocyclic Formals. IV. Macrocyclic Formals as Complexing Agents

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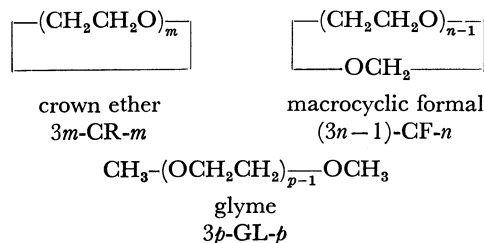
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Eleven to twenty membered macrocyclic formals have been synthesized from the corresponding polyethylene glycols and paraformaldehyde. Their activating efficiency has been measured in nucleophilic substitution reactions with alkali metal ions as counter ions. These macrocyclic formals were not as good complexing agents as crown ethers, but were much better than open chain polyethers which had the same number of oxygen atoms. In the reaction of butyl bromide with alkali metal acetate, 1,3,6,9,12,15-hexaoxacycloheptadecane was several times more effective than pentaethylene glycol dimethyl ether.

Macrocyclic compounds, such as crown ethers and cryptands, have been extensively studied in recent years as powerful complexing agents specially for alkali metal ions.¹⁻¹² The authors have been interested in the polymerization reaction of macrocyclic formals having ether oxygens besides acetal oxygens. Macrocyclic oligomers were formed in the early stage, then high polymers were formed in the polymerization of macrocyclic formals.¹³⁻¹⁷ There might be the possibility that the propagating cationic species was activated by macrocyclic oligomers already formed in the system through complexing in order to propagate. Thus, interest has been shown in the complexing ability of such macrocyclic formals with cations.

Macrocyclic formals from polyethylene glycols have the structure in which one of the ethylene groups of the crown ethers is replaced by a methylene group. They can be easily synthesized from the corresponding polyethylene glycols and paraformaldehyde by condensation and depolymerization at elevated temperatures in the presence of an acid *e.g.* *p*-toluenesulfonic acid. One of the advantages for macrocyclic formals as complexing agents is that they can be easily decomposed by mineral acids and can be separated from the products by simple extraction. From such a viewpoint, the effectiveness of crown ethers, macrocyclic formals and glymes as complexing agents were compared in a nucleophilic substitution reaction.

In this paper, complexing agents have been abbreviated according to the common crown ether nomenclature. For instance, 11-CF-4 stands for a 11-membered macrocyclic formal having four oxygen



atoms and 18-GL-6 stands for a glyme consisting of 18 skeletal atoms including 6 ether oxygen atoms, namely, pentaethylene glycol dimethyl ether.

Experimental

Synthesis of Complexing Agents. 1,3,6,9-Tetraoxacycloundecane (11-CF-4), 1,3,6,9,12-pentaoxacyclotetradecane (14-CF-5), and 1,3,6,9,12,15-hexaoxacycloheptadecane (17-

CF-6) were synthesized according to the reported methods.^{18,19} The crude products were purified by fractional distillation over lithium aluminum hydride. Since, 1,3,6,9,12,15,18-hepta-oxacycloeicosane could not be synthesized by a similar method, the method of ether linkage formation was used.

A 500 ml three-necked flask equipped with a mechanical stirrer, reflux condenser and addition funnel was charged with tetraethylene glycol (50 g, 0.26 mol) and tetrahydrofuran (200 ml). Stirring was commenced and aqueous potassium hydroxide (60%, 60 ml) solution was added and the solution was heated at 60 °C for one and a half hours. A solution of formaldehyde bis(2-chloroethyl) acetal¹⁹ (44.6 g, 0.26 mol) in tetrahydrofuran (34 ml) was then added in a stream after which the solution was refluxed and stirred vigorously for 7 days. The solution was allowed to cool and the bulk of the tetrahydrofuran was evaporated on a rotary evaporator. The resulting slurry was diluted with dichloromethane (170 ml). The upper organic layer was separated and washed with water (40 ml) in order to remove unreacted tetraethylene glycol. This water layer (40 ml) was extracted twice with dichloromethane (10 ml) and the extract was combined with the organic layer. The combined organic solution was dried with calcium chloride and the solvent was evaporated off. The residue was distilled under reduced pressure to give 7.8 g of a crude product (152—165 °C/0.2 mmHg). The crude product was redistilled over lithium aluminum hydride.

20-CF-7: bp 142—144 °C/0.2 mmHg yield 3.4 g, 4.5%. IR (NaCl, cm⁻¹) 2930, 2870, 1460, 1360, 1300, 1255, 1180, 1120, 1030, 940, 850. NMR (CDCl₃, δ ppm) 4.80 (s, 2H, -OCH₂O-), 3.78 (s, 8H, -OCH₂CH₂OCH₂O-), 3.70 (s, 16H, -OCH₂-CH₂O-).

Found: C, 52.96; H, 8.22%. Calcd for C₁₃H₂₆O₇: C, 53.05; H, 8.90%. *M. W.* (VPO) 294.34 (302).

12-Crown-4 was synthesized from 1,8-dichloro-3,6-dioxaoctane and ethylene glycol according to the literature²⁰ and 2,5,8,11,14,17-hexaoxaoctadecane (18-GL-6) by the condensation between 1-chloro-3,6-dioxaoctane and triethylene glycol monomethyl ether sodium salt.

18-GL-6: bp 149—151 °C/2.5 mmHg. IR (NaCl, cm⁻¹) 2880, 1460, 1355, 1200, 1110. NMR (CDCl₃, δ ppm) 3.68 (s, 16H, -CH₂-O-CH₂-), 3.62 (broad s, 4H, CH₃OCH₂-), 3.40 (s, 6H, CH₃O-).

Found: C, 54.35; H, 9.56%. Calcd for C₁₂H₂₆O₆: C, 54.07; H, 9.84%. Other complexing agents, 15-CR-5, 18-CR-6, 12-GL-4, and 15-GL-5 were commercially supplied.

Determination of Reaction Rate in the Presence of Complexing Agent. A 20 ml round bottomed flask equipped with a reflux condenser was charged with alkali metal acetate (metal: K, Na, Li) (0.01 mol), butyl bromide (0.01 mol) a complexing agent (0.01 mol), toluene (1.0 ml) as internal standard for GLC and benzene (9 ml). The mixture was heated to reflux at a bath temperature of 90 °C. At a

given time interval, a small portion of the reaction system was extracted with a syringe and analyzed by GLC. The conversion of the reaction was determined by use of a calibration curve using toluene as an internal standard. The gas chromatograph was a Hitachi model K 23 connected with 2 m of stainless steel columns packed with 15% Apiezon grease M on Chromosorb. It was operated at 80 °C with 17 ml/min helium as the carrier gas.

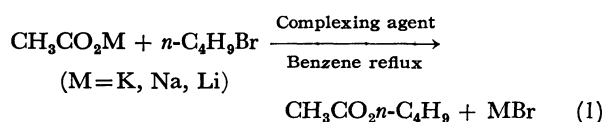
Determination of Cation Binding Efficiency of Complexing Agents.

The cation binding efficiency of the complexing agents was determined by measuring the extraction equilibrium of alkali metal picrate between dichloromethane and water. Twenty five ml of 0.1 M alkaline solution containing 8×10^{-5} mol of picric acid was extracted with 25 ml of dichloromethane and the system left to reach equilibrium. The concentration of picrate species present in the organic phase and water phase was determined by measuring the UV absorption of each phase at equilibrium using λ_{max} 357 nm (ϵ 15000) in water, λ_{max} 378 nm (ϵ 18000) in CH_2Cl_2 .²¹⁾ The UV spectrophotometer used was a Hitachi Perkin Elmer model 139 using quartz cells.

Results and Discussion

Effect of Complexing Agents on the Reaction Rate.

The effect of complexing agents in accelerating Reaction 1 was examined.



The conversion of butyl bromide or the yield of butyl acetate determined by GLC was plotted against time. A typical result has been shown in Figure 1. The conversion and the yield coincide with each other very well. The initial slope of the curve was taken as the initial rate V_0 of the reaction and the initial rates in the presence of various complexing agents have been shown in Table 1. Crown ethers were the best activating complexing agents for the reactions of potassium or sodium acetate. The initial rates decreased in the order of crown ethers, macrocyclic formals and glymes. In the case of lithium acetate, only 15-CR-5 slightly activated the reaction.

It is generally considered that the complexing agents

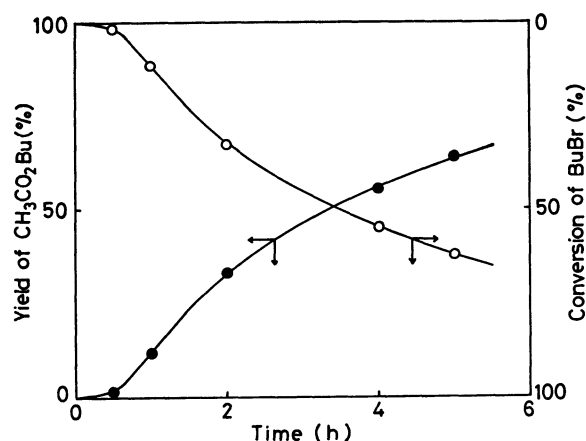


Fig. 1. Change in the quantity of *n*-BuBr and $\text{CH}_3\text{CO}_2n\text{-Bu}$ with reaction time.

TABLE 1. EFFECTS OF COMPLEXING AGENT AND CATION ON INITIAL RATE (V_0 , mol/l s $\times 10^6$)

Complexing agent	K ⁺	Na ⁺	Li ⁺
None	0.0	0.0	0.0
20-CF-7	56	0.39	0.0
17-CF-6	15	2.3	0.0
14-CF-5	0.69	0.0	0.0
11-CF-4	0.0	0.0	0.0
18-CR-6	2600	12	0.0
15-CR-5	780	13	0.81
12-CR-4	1.4	0.44	0.0
18-GL-6	2.6	0.083	0.0
15-GL-5	1.0	0.0	0.0
12-GL-4	0.25	0.0	0.0

Metal acetate 0.01 mol, *n*-BuBr 0.01 mol, complexing agent 0.01 mol, toluene 1.0 ml, benzene 9.0 ml, 90 °C.

activate the reaction by complexing with the counter cation and separating the cation from the anion species. It is also well recognized that crown ethers have specific ring sizes to fit specific cations, for instance, 18-CR-6 has a specific size for the potassium cation. In the case of macrocyclic formals, 20-CF-7 appeared to be a much better activating agent than 17-CF-6 for the reaction with potassium as the counter cation. Moreover, 17-CF-6 was a better activating agent than 14-CF-5 or 20-CF-7 for the reaction with sodium as the counter cation. Thus, in case of macrocyclic formals, the specific ring size to fit an alkali metal cation might be one ethyleneoxy unit larger than that in case of crown ethers.

Thus, in comparing the effectiveness of complexing agents in accelerating Reaction 1, it would be reasonable to compare 20-CF-7 with 18-CR-6 and 18-GL-6 and 17-CF-6 with 15-CR-5 and 15-GL-5. For the potassium cation, the ratio of the initial rates among 18-CR-6, 20-CF-7, and 18-GL-6 was 46:1.0:0.046 and for the sodium cation, it was 31:1.0:0.21. The ratio among 15-CR-5, 17-CF-6, and 15-GL-5 was 52:1.0:0.067 for the potassium cation and 5.7:1.0:0.00 for the sodium cation. It was shown that the macrocyclic formals were not as good activating agents as the crown ethers, however, they were much better than the glymes. The difference in initial rate V_0 would reflect the effective concentration of the activated anion with its counter cation complexed. In order to clarify the difference in the effectiveness among complexing agents, the complexing agents' efficiency in the extraction equilibrium of alkali metal picrate between dichloromethane and water was examined and the results have been shown in Table 2. In determining the extraction efficiency, it was assumed that the picrate did not form a complex in the water phase and that the picrate was present only in the complexed form in the dichloromethane phase.²¹⁾ As shown in Table 2, percent picrate extracted in dichloromethane phase decreased in the order of crown ether, cyclic formal, and glyme. This was the same order as in the case of the activating of Reaction 1.

The efficiency of complexing agents in extracting

TABLE 2. EXTRACTION OF PICRATE SALTS BY COMPLEXING AGENTS IN $\text{H}_2\text{O}-\text{CH}_2\text{Cl}_2$ (1:1, v/v) SOLVENT SYSTEM

Complexing agent	Percent of extracted picrate in dichloromethane		
	K ⁺	Na ⁺	Li ⁺
None	0.0	0.0	0.0
20-CF-7	14.2	1.4	0.7
17-CF-6	3.1	2.1	0.1
14-CF-5	0.1	0.1	0.0
11-CF-4	0.1	0.4	0.3
18-CR-6	88.4	7.5	2.6
15-CR-5	14.4	8.3	0.5
12-CR-4	0.5	1.3	0.1
18-GL-6	1.3	0.8	0.3
15-GL-5	0.4	0.1	0.1
12-GL-4	0.1	0.1	0.1

[Picric acid] = 8×10^{-5} M, [complexing agent] = 35×10^{-5} M, [metal hydroxide] = 0.01 M.

alkali metal cations would be controlled by ① the number of oxygen atoms in the complexing agent, ② the nature of the cation and anion of the salt, and ③ the structure of the complexing agent: cyclic or open chain and size of ring.

Let us consider a little more about these factors. Complexes are formed by the coordination of lone pair electrons of oxygen atoms to metal cations. The more oxygen atoms were contained in a complexing agent, the easier complex formation would be. When a salt is forming a complex, the easier the dissociation of the salt, the easier the complex formation. In Table 2, except 11-CF-4 and 12-CR-4, potassium picrate was extracted the most by all of the complexing agents, indicating that the ease of dissociation of the salt was the primary factor for complex formation.

The big advantage for symmetrical cyclic complexing agents in coordination is that all the oxygen atoms can participate equally. A crown ether is a cyclic oligomer of ethylene oxide and has a highly symmetrical structure. All the oxygen atoms in the ring are equivalent and the lone pair electrons can be equally directed towards the cation in complex formation. In open chain complexing agents, a pseudocyclic structure must be taken to make all oxygen atoms participate equally in coordination. This is a great disadvantage against open chain complexing agents in terms of entropy. Moreover, when it is difficult to take a pseudocyclic structure, only few oxygen atoms can participate in coordination leading to weak complex formation. In cyclic formal rings, the two acetal oxygens are not equivalent with other ether oxygens and the lone pair electrons on the acetal oxygens can only with difficulty coordinate to the metal cation. This means the effective oxygens for coordination are less than actual oxygens in the molecule.

It is also well recognized that the size of the ring is an important factor in order to form a strong complex. The ring sizes of 17-CF-6 and 14-CF-5 would be smaller than those of 18-CR-6 and 15-CR-5, respectively and the most suitable cyclic formals for potassium and sodium cations would be 20-CF-7 and 17-CF-6, respec-

tively. This situation is well shown in Table 2. The percentages of potassium picrate extracted into the dichloromethane phase were 14.2 and 3.1, for 20-CF-7 and 17-CF-6, respectively. Moreover, the percentages of sodium picrate extracted were 1.4, 2.1, and 0.1 for 20-CF-7, 17-CF-6, and 14-CF-5, respectively. When the efficiency of cyclic formals was compared with that of the crown ethers, the low efficiency of the cyclic formals was apparent. This might indicate the importance of the exact agreement of the ring size with cation size and symmetry of the ring.

TABLE 3. EFFECTS OF COMPLEX CONCENTRATION ON INITIAL RATE, V_0/C (s^{-1})

Complexing agent	K ⁺	Na ⁺	Li ⁺
None	0.0	0.0	0.0
20-CF-7	4.7	0.33	0.0
17-CF-6	6.1	1.4	0.0
14-CF-5	6.9	0.0	0.0
11-CF-4	0.0	0.0	0.0
18-CR-6	36	2.0	0.0
15-CR-5	67	1.9	2.0
12-CR-4	3.3	0.44	0.0
18-GL-6	2.6	0.14	0.0
15-GL-5	3.3	0.0	0.0
12-GL-4	2.5	0.0	0.0

Assuming that the percentage of picrate extracted into the dichloromethane phase is proportional to the concentration of the complexed species in the reaction system, V_0/C (V_0 : initial rate in Table 1, C : concentration of picrate extracted in Table 2) was taken as the relative standard of the reactivity of the complex, the values of which have been shown in Table 3. The values are in the order of 10^1 for the most effectively activated potassium-18-CR-6 or 15-CR-5 systems and in the order of 10^0 for the moderately activated potassium-20-CF-7 or 17-CF-6 and sodium-18-CR-6 or 15-CR-5 systems. The value was less than 1 for the other slow reaction systems. This might indicate that in the effectively activated systems, not only the concentration of the complex but also the reactivity of the complex was high. It would be reasonable to consider that the easier the dissociation of the salt was and the stronger the complexing agent coordinated to the cation, the higher the concentration of the complex was and the looser complexed ion pair became. The looser ion pair would have a higher degree of nucleophilicity and effectively activate the substitution reaction.

The effectiveness of the macrocyclic formals as complexing agents was not sufficiently high compared with the crown ethers in the nucleophilic substitution reactions. However, they were much more efficient complexing agents than the open chain polyethers.

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