Influence of the polymer on an anionic activation reaction promoted by a supported crown ether

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The reaction of alcohols with tetra-o-acetylbromoglucose in the presence of silver nitrate (Koenigs–Knorr reaction) is re-examined. The influence of several crown ethers, cryptands and supported ligands are studied. With t-BuOH, the reaction leads to a mixture of sugar nitrate and glycoside. We discuss the yield and the selectivity obtained with free and immobilized ligands. Supported macrocycles which assist the reaction increase the glycoside formation. The polymer effect on the selectivity is explained in terms of steric hindrance.

(Keywords: polymer supported reagent; polymer supported crown ether; crown ether; polymer effect; anionic activation; Koenigs–Knorr reaction)

INTRODUCTION

In recent years, the immobilization of a reagent on a polymeric support has attracted much attention and various applications in organic synthesis have been reported[1–6]. Soluble or bead form polymers have been used to carry out a single or a series of reactions. Supported reagents can mimic homogeneous conditions. For example, reactions which require either a dilution of sites or, on the contrary, concentration, can be carried out with insoluble polymeric supports. In addition other advantages, such as easy work up and recycling have been pointed out.

New separation processes of biological substrate mixtures or metal ions have been made possible by advances in the synthesis of selective ion exchange polymers[7]. Crown ethers and cryptands have been grafted onto resins or incorporated into polymeric chains[8–13] and their unique complexation behaviour towards alkali and alkaline earth ions have led to various applications in analytical and synthetic chemistry[14–16]. Many chemical reactions can be influenced by these reagents[17–19]: by complexing the cation of a salt, an enhancement of the reactivity of the anion may result. The potential applications to the anionic activation of the polymers containing crown ethers have also been explored[20–23].

Linear polyethers can also complex alkali ions but they are not as effective complexing agents as coronands or cryptands. Nevertheless, these polymers have been used as soluble (also in the form bound to a styrene/divinylbenzene matrix) recoverable phase transfer catalysts[24–31].

The ion binding properties and the catalytic activity of the supported macrocycle depends on many variables such as spacer length, capacity, polarity and structure of the resin[20–22,32–33].

The influence of the length of the spacer on the activity of supported crown ethers, cryptands and phosphonium salts used as catalysts in anion promoted phase transfer reactions, has been studied by Montanari[20] and Tomoi[34] who reported an increase in activity approaching that of the small analogue catalysts when they are bound with a long chain to the polymeric support.

We have studied the extraction of various cations by the diaza-18-crown-6 grafted to a polyacrylamide gel and we have showed that the resin has a great affinity for cations such as Ag^+, Hg^{2+} and Cd^{2+}.[11] We were interested in the complexation ability of this resin and therefore several kinds of copolymers have been synthesized to study the influence of the grafting on the activity of the macrocycle for a ligand assisted reaction. For this purpose, we selected a model reaction in which one of these salts and a macrocycle or a cryptand are involved.

LIGAND ASSISTED REACTION

In the Koenigs–Knorr reaction, a brominated sugar reacts with an alcohol in presence of a silver, mercury or cadmium salt to form a glycoside[35]. Knoechel et al.[36–37] studied the influence of a macrocycle on this reaction. They showed the macrocycle promotes a very fast reaction, but they also observed the formation of a byproduct: the nitrate ester of the sugar.
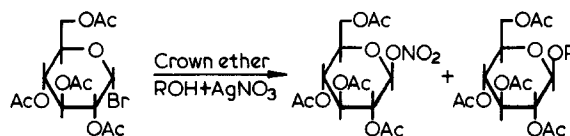
The selectivity is dependent on the nature of the macrocycle, the alcohol bulkiness and the medium dielectric constant. An increase in the nitrate derivative formation is observed with an increase of the Ag^+/macrocycle complex stability or an increase in the hindrance of the alcohol. The amount of the nitrate derivative can

reach 36% when t-butanol reacts in the presence of the [222] cryptand.

Consequently, the Koenigs–Knorr reaction seems especially interesting due to its environmental sensitivity on both yield and selectivity. In addition, it has a synthetic utility for glycoside formation.

Here we have re-examined the reaction in presence of free crown ethers, polymeric crown ethers and crown ethers covalently attached to a resin with a view to comparing the resultant activity of the supported reagent with the small analogue.

The reaction depends on many variables and the parameters we investigated concern the nature of the components of the reaction mixture; alcohol, solvent, macrocycle, polymer and the amount of added macrocycle.

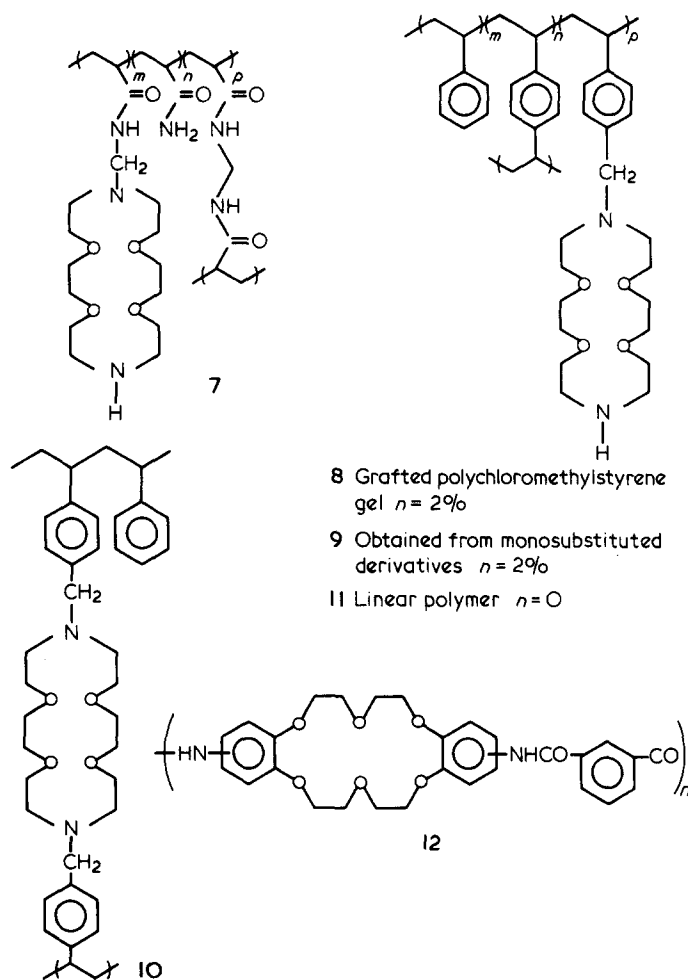Six macrocycles with different substituents, rigidity and hetero-atoms were selected.

1

2

3

4 $R_1 = R_2 = H$

5 $R_1 = \phi CH_2, R_2 = H$

6 $R_1 = R_2 = \phi - CH_2$
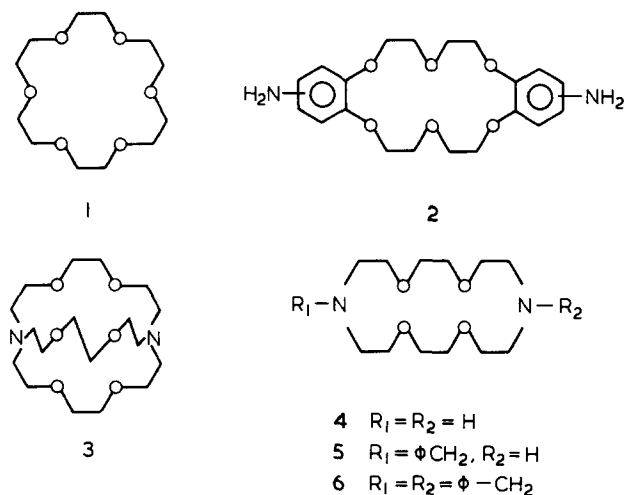
Compounds **3** and **4** were used by Knoechel[36].

The diaza-18-crown-6 was attached either to a polyacrylamide **7** or a polystyrene gel **8** to probe the influence of the backbone polarity. The functionalization of the styrene/divinylbenzene resin was carried out under phase transfer conditions. Polymer **9** was prepared by reacting chloromethylstryrene with the diaza-18-crown-6. The monosubstituted crown ether was separated and copolymerized with styrene. Copolymer **10** was prepared from the disubstituted crown derivative. The modification of linear polychloromethylstyrene ($\overline{M}_n = 17\,000$) was effected by grafting the macrocycle in DMF (copolymer **11**). Polymers of various capacity have been used and they all give the same results. In addition a polyamide with the macrocycle incorporated in the backbone was used **12**. The polyamide was obtained from diaminodibenzo-18-crown-6 and isophtaloydichloride.

EXPERIMENTAL

Materials

The 18-crown-6 and cryptands [2,2] and [222] are commercial products (MERCK). The diaminodibenzo-18-crown-6 was a gift from Dr M. Hiraoka (Nippon Soda Co.). Styrene (MERCK) is a product 99% stabilized with ter-butylcatechol. Divinylbenzene was a technical product (MERCK) containing 50% DVB and stabilized with ter-butylcatechol. Chloromethylstyrene (FLUKA) was distilled before use. The tetra-acetylbromoglucose (KOCH-LIGHT) is purified on a silica gel column eluting

7

8 Grafted polychloromethylstyrene gel $n = 2\%$

9 Obtained from monosubstituted derivatives $n = 2\%$

11 Linear polymer $n = 0$

12

10

with 1/1 cyclohexane/ethylacetate. Silver nitrate (PRO-LABO, analytical grade), is carefully powdered to 30 μm particles.

Polymerization

The polymerization was carried out in a water suspension at 90°C[38]. A typical copolymerization is as follows: in water (125 ml) with 0.1% surfactant (sodium lignosulphonate), a dispersive agent (carboxymethylcellulose) (1%) and NaCl (44 g) are added. The vessel is flushed with nitrogen and heated to 70°C. A mixture containing styrene (34 g), commercial DVB (2 g), chloromethylstyrene (14 g), benzylalcohol (44 g) as diluent and AIBN (0.8 g) is then introduced. The temperature is raised to 75°–80°C and the reaction is run for 6 h. The beads are decanted, washed with water, MeOH, THF and dried.

The linear copolymer styrene/chloromethylstyrene was prepared in solution in toluene with azobisisobutyronitrile as initiator. The copolymer was precipitated in MeOH. It was characterized by g.p.c. in THF ($M_n = 17\,000$, $\overline{M}_p = 33\,000$) and contains 2meqCl/g.

The synthesis and the modification of the polyacrylamide gel with the diaza-tetra-oxa-macrocycle have been previously described[11]. The polyamide **12** was prepared by polycondensation in HMPT at room temperature. To 0.005 moles diamino-dibenzo-18-crown-6 dissolved in HMPT (20 ml) purged with nitrogen, 0.005 moles isophtaloyldichloride in HMPT (10 ml) were slowly added. The reaction was carried out for 16 h and the copolymer precipitated in MeOH, separated and extracted with acetone in a soxhlet column.

Compounds **5** and **6**, the vinylanalogues and the

modification of the chloromethylated gel was carried out under phase transfer catalysis conditions. Typically, for the preparation of resin **8**, the beads (1 g (2meqCl)) were swollen in dichlorobenzene. Then diaza-tetra-oxa-macrocycle (1 g (4 mmole)), tetrabutylammonium hydrogenosulphate (0.6 g) and LiOH (0.6 g) dissolved in H_2O (6 ml) were added. The mixture was stirred for 48 h at 40°C. The beads were filtered and washed with H_2O, MeOH and THF and dried under high vacuum conditions. The capacity, determined by titration and microanalysis, was 0.8 meq/g; with 70% yield.

Reaction procedure

The Koenigs–Knorr reactions were carried out under argon in a dried flask. All reagents were carefully dried before used. In t-butylalcohol (2 ml), $AgNO_3$ (85 mg (0.5 mmole)) and 0.5 mmole of the ligand were added. After 5 min sugar (206 mg (0.5 mmole)) in t-butylalcohol (1 ml) was introduced with a syringe into the reaction flask. After another 5 min period, the excess of t-butylalcohol was evaporated by freeze drying. The residue was worked up with 0.8 ml $CDCl_3$ and filtered and the selectivity was determined by ^1H n.m.r.

For testing our procedure, in some experiments, $CDCl_3$ was substituted with anhydrous ether and the crude products were isolated (yield 96%). The two processes gave the same results.

Following these experimental conditions and using diglyme, pure nitrate derivative has been isolated.

The polystyrenic support was recycled by washing with a 10% sodium thiosulphate solution, water, MeOH and THF. No trace of silver ions could be detected.

RESULTS AND DISCUSSION

In order to probe the model reaction, that is the glycoside and/or the nitrate derivative formation, we selected 2 alcohols which differ by steric hindrance and polarity; these were methanol and t-butylalcohol.

The reaction involves 2 steps:

(1) the alcohol, $AgNO_3$ and the ligand are mixed for 5 min allowing the complexation equilibrium to be reached.

(2) the sugar is added.

Reactions in presence of free crown ethers

(i) Methanol, a small and very reactive molecule, leads to the glycoside derivative with a quantitative yield when either small molecules or polymers are added.

$$\text{sugar} + \text{MeOH} \xrightarrow[\text{AgNO}_3]{\text{crown ether}} \beta \text{ glycoside}$$
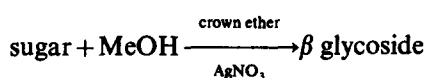
The reaction is fast and achieved in 2 min at 0°C. With methanol, whatever the ligand, we observed an acceleration of the reaction but no effect on the selectivity.

(ii) t-Butylalcohol, a bulky reagent, leads to a mixture of the glycoside derivative and the nitrate one, the selectivity depending on the macrocycle:

$$\text{sugar} + \text{t-BuOH} \xrightarrow[\text{AgNO}_3]{\text{crown ether}} \beta \text{ ONO}_2 + \beta \text{ glycoside}$$
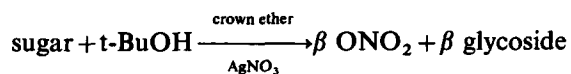
The product distribution is independent of the ligand concentration. Experiments were mostly with a 10%

ligand/sugar ratio, as Knoechel described[36], and we generally observed a yield decrease only when this ratio becomes less than 1%.

Note in *Table 1* that a low yield is obtained with compound **2**. This result might be due to the poor solubility of compound **2** in t-butylalcohol.

The reaction is fast and generally achieved within 5 min at room temperature and after that time we observed no influence on the yield or on the selectivity. Results are given *Table 1*.

We can note discrepancies between our results and those reported by Knoechel on the selectivity and the yield of the reaction. We found that in the presence of crown ethers **3** or **4**, the reaction leads almost exclusively to the nitrate derivative, contrary to results given elsewhere. A yield of 50% was reported with t-BuOH and dibenzo-18-crown-6 as the catalyst. No information is given on the other experiments.

A good or bad yield, depending on the cryptand, was indicated for the formation of the nitrate derivative in diglyme. We always obtained the nitrate with a yield higher than 85%.

We think the discrepancies can be explained by the experimental procedure used to characterize the reaction products. In Knoechel's work the selectivity was determined by polarimetry after addition of aqueous $NaHCO_3$ to the reaction mixture and separation by chromatography. With this procedure, there is a possibility of the esters hydrolysing and checking by i.r. spectroscopy the simple and rapid disappearance of the nitrate covalent band under wet conditions supports this hypothesis.

The relation between the stability of the complexes and the selectivity is also worth mentioning.

Ag^+ cation interacts favourably with a soft donor like N. Complex constants have been reported for some of the crown ethers and cryptands used here[39–40]. As expected it is low for 18-crown-6 and fairly high for the cryptands. 18-crown-6 $K_s^{Ag^+} = 1.6$; [2,2] $K_s^{Ag^+} = 7.80$; [2,2,2] $K_s^{Ag^+} = 9.6$ in water at 25°C.

Crown ethers **1** and **2** give poor complexes with Ag^+ and the anion is partially activated. The reaction gives 70% nitrate and 30% β glycoside. Crown ethers **3** and **4** are better ligands for Ag^+ than the latter two and they enhance the anion activity and the formation of the nitrate is increased. Crown ethers **5** and **6** show intermediate behaviour. The mono- and disubstitution decreases the complexing ability of the ligand and we observe a decrease in the nitrate formation.

Addition of a solvent to the reaction mixture favours the nitrate derivative. DMF was used because it has the same functional group as the polyacrylamide support and CH_2Cl_2 and toluene are good solvents for polystyrene.

Table 1 Selectivity in the presence of various macrocycles

Crown ethers	βONO_2	βOt-Bu	Yield
1	70	30	100
2	70	30	44
3	95 (37)*	5 (63)*	100
4	93 (4)*	7 (96)*	100
4 + DMF	96	4	100
5	74	26	76
5 + CH_2Cl_2	86	14	100
6	91	9	80
6 + CH_2Cl_2	90	10	100

* Data from the literature, see refs. 36–37

Reactions in presence of polymeric crown ethers

When a polymer is used to assist the reaction, a triphase system is involved (*Figure 1*). In the two phase system, fine silver nitrate particles are quickly dissolved by the crown ether and the reaction is achieved in less than 2 min. In the triphase system, we assumed a longer time to reach the complexation equilibrium. Several runs of varying times of complexation and reaction steps, were carried out. We observed a complete reaction using two 5 min periods.

The selectivities obtained with the immobilized crown ethers are shown in *Table 2*. Several features can be pointed out from the comparison of the results obtained with polymeric ligands and small analogues.

Table 1 shows large differences in selectivity, depending on the complexing behaviour of the macrocycle. However, on the contrary, in the absence of solvent, all polymers (7 to 12) have the same selectivity. The glycoside formation increases and glycoside and nitrate derivative are formed in nearly equal quantities. A change in the yield is observed, depending on the polymer.

When a swelling solvent of the gel is added, the selectivity is greatly affected and the yield reaches 100%. The formation of the nitrate derivative increases and the selectivity tends to be similar to that obtained with the smaller analogues. The complexation of the macrocycle does not seem to be affected by immobilization on a support. When the polymer is swollen, the macrocycle is more flexible which favours interaction with the cation. The activation of the anion is similar to that promoted by the small molecule.

The effect of a polymer as cosolvent has been reported in the literature[41]. We did not notice any influence of the micro-environment polarity on the competitive reactions
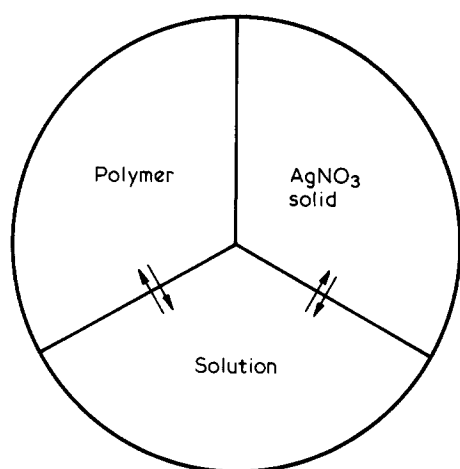
and our interpretation is based on steric effects of the polymer.

There is competition between both nitrate and t-butylalcohol. $AgNO_3$ gives a complex with the crown ether. The sugar comes close to one face of the macrocycle and the anion is located on the other face. When the cryptand is bound, the mobility of the anion is hindered by the polymer framework and this effect favours the approach of t-BuOH: a greater proportion of glycoside is therefore obtained. When the reaction is carried out in CH_2Cl_2, the amount of nitrate derivatives increases. The solvent swells the resin and the reagent sites become more accessible. The amount of nitrate derivative also increases when the polyacrylamide resin is swollen in DMF. Without solvent, the t-butylalcohol is a bad solvent for the gel and the chains collapse. In addition, the diffusion of the reagents in the gel is hindered.

CONCLUSION

On a model reaction, assisted by a polymeric ligand, we have shown that the polymer framework is an active partner. With MeOH as reagent, the reaction studied leads quantitatively to a sole derivative whether the crown ether is supported or not. With a bulky alcohol and without solvent, the role of the macrocycle, which assists the substitution reaction, is perturbated by the rigidity of the matrix. Two products are formed and the selectivity seems to be independent of the polymeric ligand. The glycoside is formed with a good yield. In a good solvent for the polymer, the nitrate formation increases, and the selectivity comes close to that observed with the smaller ligands.

This work points out the environmental effect of the polymer. In polymer supported synthesis, the influence of the polymer backbone is an important parameter, particularly in regard to small molecules, but difficult to study. We think that this point can be precisely investigated using this particularly sensitive reaction: a change of the texture of a resin would induce a change in both yield and selectivity.

Figure 1 Polymer crown ether triphase system

Table 2 Selectivity in presence of immobilized macrocycles

Polymers	βONO_2	$\beta Ot\text{-}Bu$	Yield
7	57	43	100
8	57	43	100
9	54	46	98
10	59	41	94
11	56	44	86
12	59	41	89
7 + DMF	95	5	100
8 + CH_2Cl_2	75	25	100
8 + ϕCH_3	73	27	100
11 + CH_2Cl_2	89	11	100

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