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Polycarboxylate Crown Ethers: Synthesis, Complexation, Applications

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Abstract. Crown ethers derived from tartaric acid present a number of interesting features as receptor frameworks and offer a possibility of enhanced metal cation binding due to favorable electrostatic interactions. The synthesis of polycarboxylate crown ethers from tartaric acid is achieved by simple Williamson ether synthesis using thallous ethoxide or sodium hydride as base. Stability constants for the complexation of alkali metal and alkaline earth cations were determined by potentiometric titration. Complexation is dominated by electrostatic interactions but cooperative coordination of the cation by both the crown ether and a carboxylate group is essential to complex stability. Complexes are stable to pH 3 and the ligands can be used as simultaneous proton and metal ion buffers. The low extractibility of the complexes was applied in a membrane transport system which is a formal model of primary active transport.

Key words. membrane transport, metal cation binding, tartaric acid.

1. Introduction

The field of molecular recognition by synthetic receptors arose from the problem of alkali metal cation complexation. Initial studies by Pedersen on crown ethers [1], followed by the cryptands of Lehn [2] and more recently Cram's spherands [3] illustrate an increasingly sophisticated and successful approach to the recognition of spherical cations. To a certain degree the problem may be regarded as 'solved', as stable and selective complexes of the alkali metals and alkaline earth cations are now well described. However, with respect to recognition coupled to other supramolecular functions such as transport, the general problem remains unresolved in many important aspects. From a practical viewpoint, the synthetic complexity of some ligands precludes their use. In other applications the complexation kinetics, or the pH range of optimal complexation, may not be suitable. Thus the continued investigation of problems in spherical cation recognition appears to be justified.

From this perspective, crown ethers derived from (+)tartaric acid possess a number of appealing features as frameworks for the construction of specific complexing agents. The basic skeletons are readily assembled via reliable procedures [4, 5] and the carboxylate groups provide an easy entry into a range of derivatives [6, 7]. Secondly, tartarate-derived groups show a marked preference for occupying axial positions on the macrocycle [4, 8, 9] thereby restricting conformational mobility [9, 10]. Finally, the presence of charged groups on a macrocycle periphery leads to markedly enhanced cation complexation relative to uncharged forms [4, 10].

We have been exploring the chemistry of this class of compounds for the past few years with a focus on synthesis and on a detailed examination of cation

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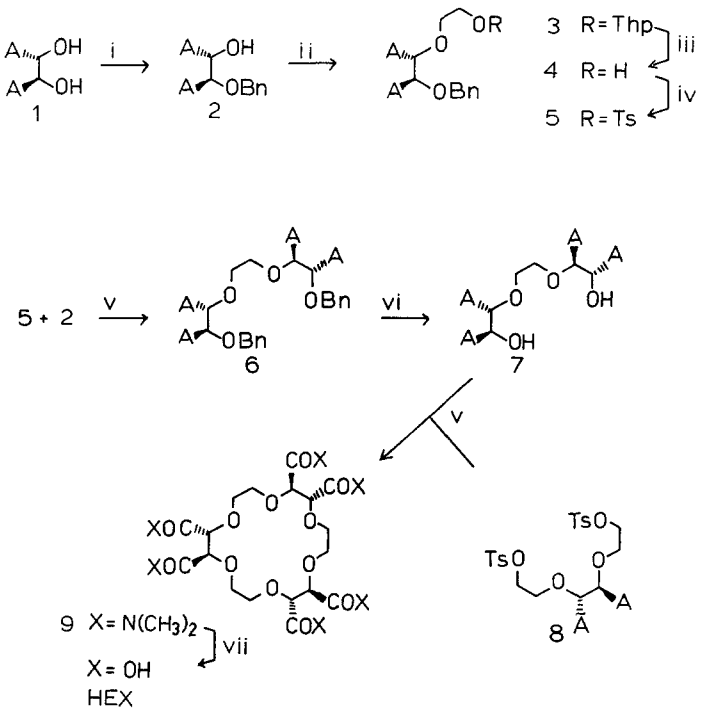
complexation. As well, we have investigated applications in which stable alkali metal or alkaline earth cation complexes are required, particularly in aqueous and acidic solution. This report surveys some recent progress in all these areas.

2. Synthesis of Polycarboxylate Crown Ethers

The central reaction is, of course, the Williamson ether synthesis. Early reports on the preparation of tartaric acid ethers [11], suggested that the base thallous ethoxide, (TlOEt), was essential to avoid epimerization of the chiral centers. The first syntheses thus utilized this base in dimethyformamide (DMF), and oligo-ethylenglycol diiodides for the preparation of di- and tetra-carboxylate crown ethers [4, 12]. More recently, we found that by strict control of stoichiometry, sodium hydride could be used successfully to displace tosylate without loss of chiral integrity [5]. Scheme 1 shows a recent synthesis of an 18-crown-6 hexaacid from three units of (+)tartaric acid [13]. This route illustrates all the key features in the syntheses of polycarboxylate crown ethers.

Tartaramide (**1**) in DMF was treated with one equivalent of NaH and then with excess benzylbromide to give the monobenzyl ether **2**. Compound **2**, like many other synthetic intermediates encountered, possesses a convenient hydrophilic/



Scheme 1. Synthesis of an 18-crown-6 Hexaacid.
Reagents: (i) (1) NaH (1 equiv.)/DMF, (2) BnBr (excess); (ii) (1) TlOEt/DMF, (2) $BrCH_2$ CH_2OThp; (iii) H_3O^+/MeOH; (iv) $TsCl/Et_3N/CH_2Cl_2$; (v) NaH/DMF; (vi) H_2Pd–C; (vii) H_3O^+/reflux. Abbreviations: A = $Me_2NC(=O)$—, Bn = benzyl, Ts = tosyl, Thp = tetahydropyranyl.

hydrophobic balance. Thus **2** can be purified by a simple sequence of solvent extractions, initially from hydrocarbon solvents into water and then into chlorocarbon solvents. Coupling of **2** with the tetrahydropyranyl ether of 2-bromoethanol was achieved using TlOEt in DMF to give **3**, purified by chromatography. Hydrolysis gave the alcohol **4** which was directly converted to a tosylate **5**. A second equivalent of the sodium salt of **2** (NaH/DMF) was then treated with **5** to yield the half crown **6**, which was purified by chromatography and then deprotected to give the diol **7**. A directly comparable sequence from **1** without monoprotection gave the ditosylate **8** [14]. The final macrocyclization again utilized NaH to yield the hexaamide **9** which was finally deprotected in refluxing aqueous HCl to give the hexaacid (HEX).

Although the hexaacid crystallized readily from water, it was soon apparent that it was not pure, but contained alkali metal and alkaline earth cation impurities. Even repeated crystallization from acid failed to remove these impurities. Finally, ion exchange using Dowex resin (extensively washed with high purity acid) and doubly distilled water as eluent, gave a metal-free sample of HEX [13]. The crystal structures of HEX and its Na^+, K^+, Tl^+ and Cs^+ complexes readily explain the strong propensity to resist purification by crystallization [15]. The free ligand HEX crystallizes as the tetrahydrate in which a hydrogen bonded dimer of water molecules is bound with the ligand cavity. Cation binding results in loss of a proton from the ligand and loss of one water molecule from the cavity. The water position is occupied by the cation, well above the plane of the macrocycle. The close oxygen contacts with the cation involve the ligand carboxylate, the remaining water and, at longer distances, the ether oxygens [15]. All complexes investigated are approximately isostructural with the free ligand thus the crystallization readily proceeds with inclusion of metal impurities.

3. Cation Complexation by Polycarboxylate Crown Ethers

The cation complexation behavior of the carboxylate crown ethers illustrated in Figure 1 was investigated by potentiometric titration. The principles have been discussed previously [10, 12]; the primary constants determined are cumulative

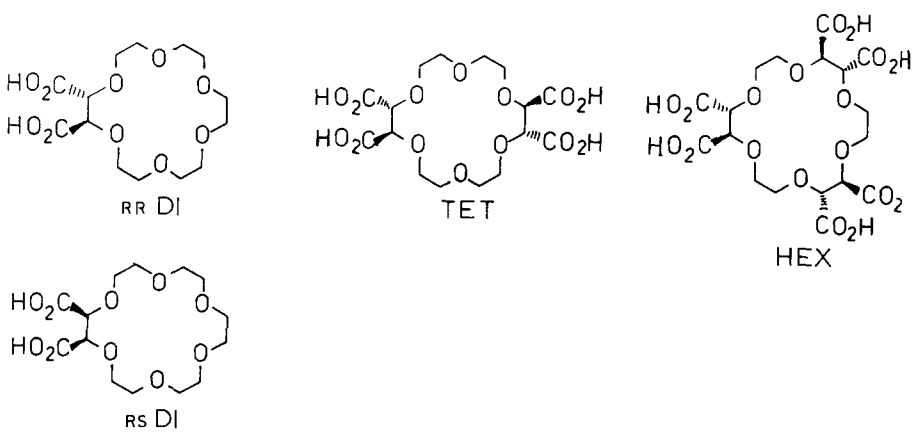


Fig. 1. Structures of the ligands considered with abbreviated names.

association constants which may be used to calculate stepwise formation constants for the 1 : 1 association of a cation with the ligand at various levels of protonation. The experimental procedure involves the pH-metric titration of the ligand as the free acid, with base (Me_4NOH). The resulting titration curve is analysed [16] to yield the ligand pK_as. Metal ion is then added to the system and a titration is repeated on the mixture. The titration curve, together with the previously determined pK_as, is then analysed [16] to yield the cumulative formation constants of the cation complexes.

Results for the four ligands of Figure 1, at various levels of protonation, are given in Table I [13]. The data clearly reveal the dominant role that electrostatic interaction plays in the complexation process: (i) There is a general trend to greater stability constant for a given cation as ligand charge increases (down a column), (ii) there is a clear trend which favors divalent over monovalent ions at all levels of ligand protonation, and (iii) many ligand/cation combinations exhibit a regular decrease in stability constant as the ligand is protonated. In addition, however, there are some clear structural effects. Most notable is the expected 'hole-size' effect [13]; in the present case, the larger cations are favored relative to smaller cations. This occurs despite the greater surface charge density of the smaller cations which would enhance any electrostatic interaction with the ligand.

The most important irregularity in the data concerns the Tl^+ complexes of HEX^{6-} and TET^{4-} and the K^+ complex of HEX^{6-}. In each of these cases, ligand protonation results in substantial stabilization of the complex in direct opposition to the expectation of electrostatic stabilization. These cases are the interactions of the most highly charged ligands with the cations of the lowest surface charge density. On a purely electrostatic basis, Tl^+ and K^+ are least able to organize the carboxylate donors in the face of the strong internal repulsions between the carboxylates. The fully deprotonated ligands are thus too large to provide a suitable set of donor atoms, and too rigid to be distorted, thus the complexes are destabilized. Monoprotonation, however, relieves some intramolecular repulsions, increases ligand flexibility and results in enhanced complex stability. This is an example of the principle that the 'guest organizes the host' [17].

Table I. Logarithm of stepwise formation constants.[a]

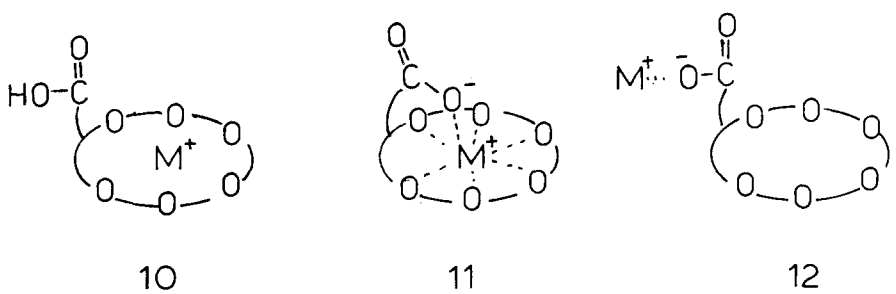
Ligand	Na^+	K^+	Tl^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
R,R-HDI^-	2.4	3.2	4.6	*	4.2	*
R,R-DI^{2-}	3.3	4.2	5.7	5.6	5.9	6.5
R,S-DI^{2-}	2.5	3.1	3.3	4.3	5.8	5.6
H_2TET^{2-}	1.9	3.4	*	*	*	*
$HTET^{3-}$	4.1	4.7	4.8	7.0	6.1	6.2
TET^{4-}	4.5	4.8	3.6	8.6	8.0	7.2
H_2HEX^{4-}	4.0	4.0	5.1	6.7	6.8	6.5
$HHEX^{5-}$	5.1	5.3	5.8	8.6	8.8	8.8
HEX^{6-}	5.4	4.1	4.4	9.8	10.4	9.5

[a] Determined by potentiometric titration at 25°, $I = 0.05$ M with Me_4NCl. Values are calculated from the cumulative formation constants for the complexes and the ligand pK_as. The symbol * indicates that the complex was not required to achieve a fit of the experimental data. Uncertainty in log $K \pm 0.2$.

Since monoprotonation relieves the irregularity, it is possible that one additional donor site, a carboxylate, is required by the cation and the ligands act as seven oxygen donors. In this view, complexes of moderately charged ligands, or of cations of high surface charge density, could easily achieve seven coordination. In the Tl^+ and K^+ cases noted above, the energetic 'cost' of seven-coordination involving ligand distortion is inadequately balanced by the metal-ligand interaction energy gained, hence the lower stability constant.

The question of carboxylate participation in cation binding has been extensively examined. Evidence from infrared and nuclear magnetic resonance [10], from electron spin resonance [9] and from potentiometric titration experiments [10, 18] suggests that direct, cooperative carboxylate-cation interactions occur. The method of Eyring and coworkers [18] can be applied to the data of Table I to estimate the extent of this cooperative interaction. The method separates the total binding energy into three contributions as illustrated in Figure 2: (i) a cavity term (**10**), involving only the cation association with the neutral crown ether, (ii) an electrostatic term (**12**), involving only coulombic interactions between the ligand and the cation, and (iii) a cooperative term (**11**) involving the two effects together as implied by a coordinative carboxylate–metal cation interaction. For the majority of the cases of Table I, the cooperative term accounts for approximately half of the total binding energy, with electrostatic and cavity effects making up the other half [13]. These latter depend closely on the ion size, thus large cations (K^+, Tl^+, Ba^{2+}) have large cavity contributions and small electrostatic contributions. The converse applies to the smaller cations. The principal exceptions are the complexes of Ca^{2+}. With a very high surface charge density, Ca^{2+} complexation is dominated by the electrostatic factor with only minor (10%) contribution by the cooperative factor [13].

The data of Table I provides other insights into the complexaton process. A comparison of the configurational isomers *R,R*-DI and *R,S*-DI reveals that the complexes of the latter are uniformly less stable. As noted in the introduction, the *RR*-system derived from (+)tartaric acid results in an axial disposition of the carboxylates. The *RS*-system can only involve an axial–equatorial disposition of carboxylates, probably equilibrating between two equivalent forms in the free ligand. If cation complexation results in coordination by a ligand carboxylate as argued above, then this would freeze one conformation of the ligand. Complexation



10 11 12

Fig. 2. Modes of cation-ligand association: **10** – cavity term; **11** – cooperative interaction; **12** – coulombic interaction.

would then be entropically less favored than in the *RR*-system. At the same time, the equatorial-CO_2^- is further away from the cation in the macrocycle and the electrostatic stabilization afforded would be less as well.

To summarize the overall picture of cation binding: these ligands normally bind cations with cooperative crown ether and carboxylate donor interactions. This results in a trend favoring larger cations. However, the complexes are also stabilized by a general electrostatic interaction of the ligand and the cation. This will be greatest for the smallest cations. Thus as ligand charge increases, a trend favoring large cations reverses to a trend favoring small cations. As well as increasing the charge, deprotonation also rigidifies the ligand. In some cases, the complexes of the low surface charge density cations Tl^+ and K^+ are destabilized, since the energetic advantage of carboxylate coordination is insufficient to achieve ligand distortion.

4. Application of Polycarboxylate Crown Ethers

The complexes of the polycarboxylate crown ethers of Figure 1 are substantially more stable than those of their parent, 18-crown-6. The stability constants of Table I, in fact, fall into the range usually associated with cryptands 2.2.1 and 2.2.2 [19] and EDTA [20]. However, relative to these ligands, the polycarboxylate crown ethers appear as relatively indiscriminant cation complexing agents. Very little molecular recognition based on ion size difference is occurring. Nonetheless, there are a number of features of the complexation of cations by polycarboxylate crown ethers which have lead to some simple but unique applications.

4.1. SIMULTANEOUS PROTON AND METAL ION BUFFERING

Polycarboxylate crown ethers bind cations over a wide range of pH. Although the protonated complexes tend to be less stable than the complexes of the fully deprotonated ligand, nonetheless cation binding does occur, even in acidic solution (pH 3). This is in sharp contrast to the cryptands and EDTA, in which protonated complexes are vastly less stable or do not form. Furthermore, the first pK_as of these ligands are much more basic [19, 20], thus cation complexation even at pH 7 cannot be easily achieved (some very stable EDTA complexes, with Ca^{2+} for example, can form into weakly acidic solution (pH 6)).

Furthermore, the polycarboxylate crown ethers have a series of protonation equilibria, both of the free ligand and of the complexes, which extend over a range of pH in which metal ions are complexed. This results in the possibility of simultaneous buffering both protons and metal ions with a single species [21]. One example of this potential is illustrated in Figure 3. Obviously the buffering capacity of such a dilute solution is limited. Even so, the calculated buffer capacity has significant values over part of the range where K^+ is bound (pH 3–7). As an example, consider the solution of 1 mM HEX containing 0.5 mM K^+ at pH 4.5. Addition of a further one quarter equivalent of KOH, to give a total K^+ concentration of 0.75 mM, results in a pH change to 4.68 and a change in free K^+ concentration to 2.7×10^{-5}M ($> 95\%$ complexed). This type of behavior is rare, although some pH buffer components will bind transition metal ions to achieve a similar effect [21].

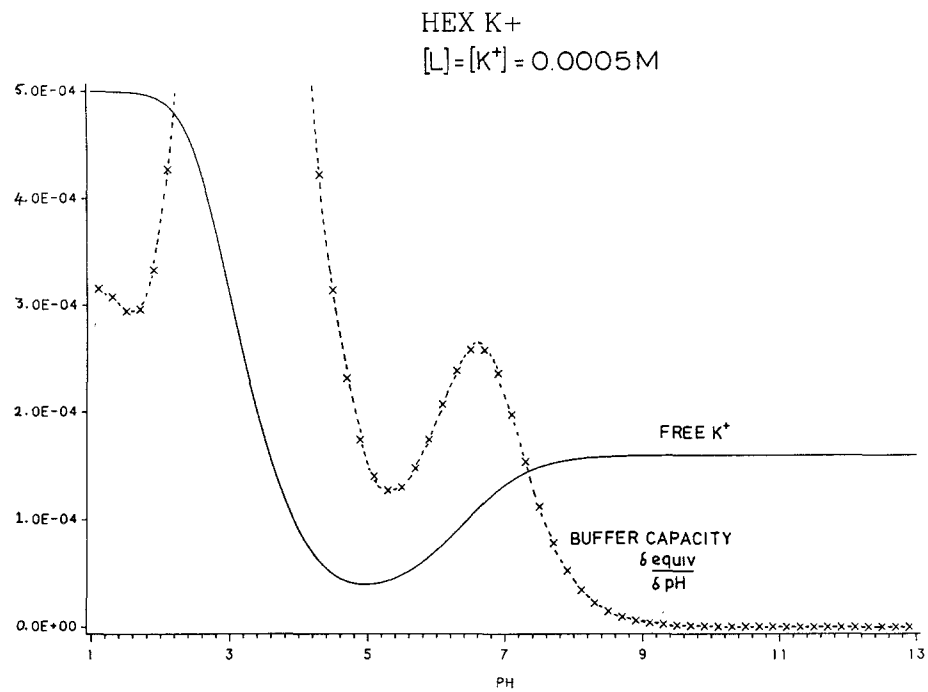


Fig. 3. Calculated free potassium ion concentration and buffer capacity as a function of pH for a 1 : 1 mixture of HEX and K^+ at 5×10^{-4}M.

4.2. MODEL OF PRIMARY ACTIVE TRANSPORT

The cation complexes of polycarboxylate crown ethers are charged, thus resist extraction into organic solvent. This is in contrast to cryptands which can be used as organic soluble membrane transport carriers of cations. Our interests in membrane transport mechanisms [10, 12, 22] lead us to consider the implications of a theoretical framework of energy transduction in membranes proposed by Goddard [23]. Within the framework, strong parallels are drawn between simple gradient pumping systems, such as are widely known for crown ether and cryptand carriers [24, 26], and systems involving reaction pumping, or primary active transport. In order to convert a gradient pumping to a reaction pumping transport system, one of the translocated species must be intercepted in the receiving phase. It is the free energy of this association which energizes the transport cycle. We wished to explore the simple thermodynamic and kinetic predictions of the model proposed [23], hence we investigated the transport cycle illustrated in Figure 4 [27]. This system is formally an example of primary active transport in which the driving force for transport is provided by the association of the transported K^+ with the crown ether dicarboxylate in the right aqueous phase. The system exploits the property of strong complex formation in water and the low extractibility of the crown ether complex in direct contrast to the properties of the cryptand carrier in the same system.

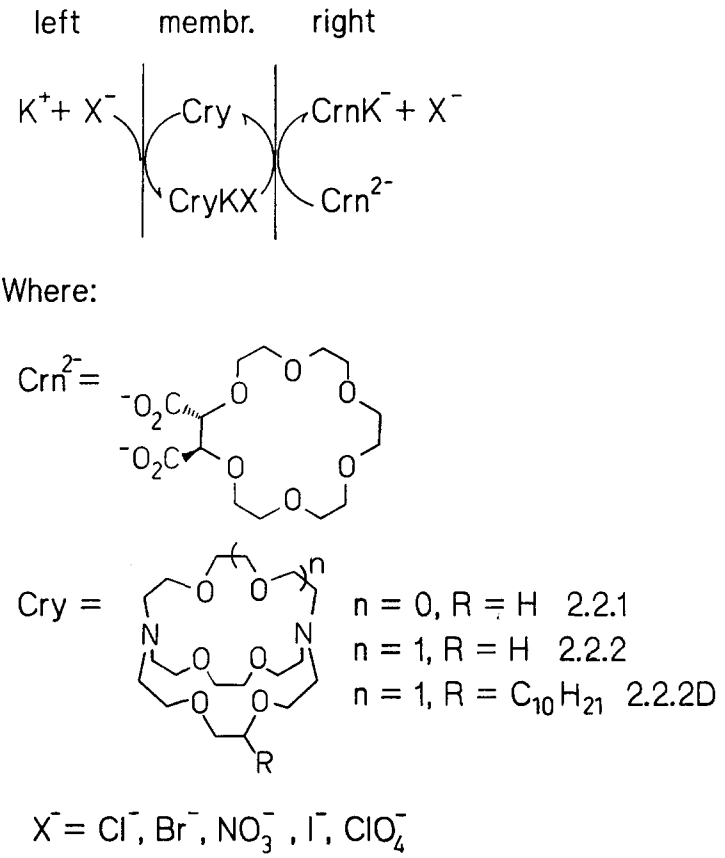


Fig. 4. Schematic mechanism of a chemical model of primary active transport (reaction pumping).

In this system, as in all systems under diffusion control [22, 24], the flux is a bell-shaped function of the extraction constant, K_{ex}, of the carrier (Cry). As illustrated in Figure 5, at low values of $\log K_{ex}$, the flux is low as only a small amount of KX is extracted into the membrane. As $\log K_{ex}$ increases, the flux increases to a maximum when the carrier is half saturated. A further increase in $\log K_{ex}$ results in a decrease in flux as the KX is held within the organic phase. The theoretical curve of Figure 5 may be calculated from a knowledge of the initial concentrations of the various species, and the value of the 1 : 1 association constant of the crown ether K^+ complex which energizes the transport [27]. The experimental points of Figure 5 were obtained from a series of experiments with the three carriers and five anions of Figure 4. In various combinations, they provided various values of $\log K_{ex}$, and gave characteristic values of the flux in the transport experiment. The excellent agreement between theory and experiment serves to encourage our use of the theoretical framework of Goddard [23] as a design tool for development of new transport systems.

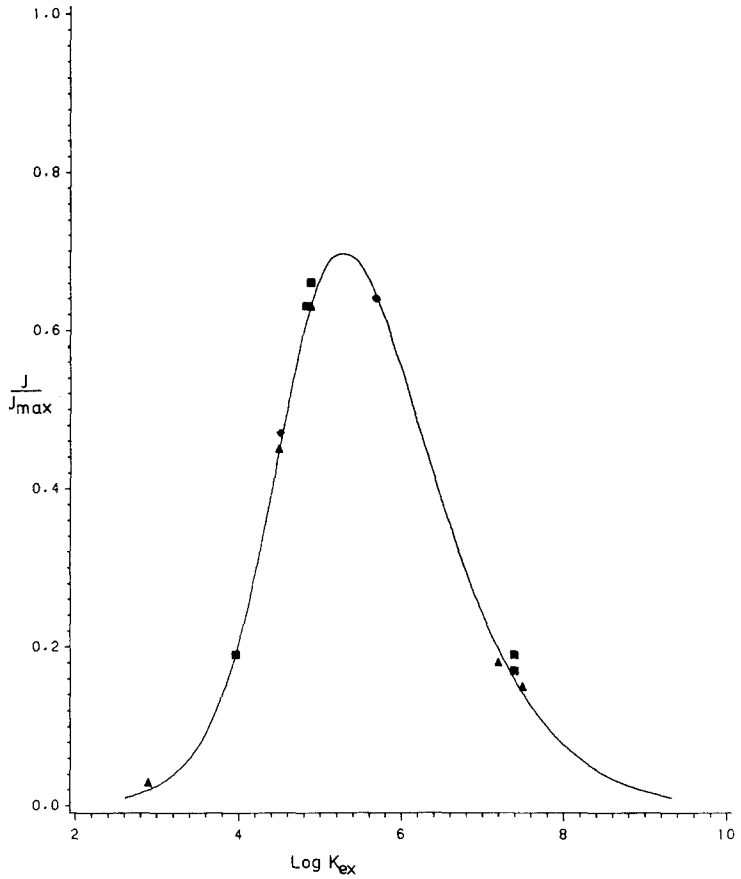


Fig. 5. Normalized membrane flux (J/J_{max}) as a function of extraction constant (log K_{ex}) for the transport system of Figure 4 [27]; 5.0×10^{-3} KX, pH 9.6; glycine/MTEAOH[11]1.0×10^{-3}M Cry in $CHCl_3$ || 5.0×10^{3}M Crn, 2.0×10^{-3}M KX, pH 9.6, glycine/MTEAOH, U-tube transport cell, stirring at 400 ± 5 rpm, 25°C. Theoretical curve calculated for 5% total transport. ■ = 2.2.2D as carrier, ▲ = 2.2.2 as carrier, ◆ = 2.2.1 as carrier.

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