LIPOPHILIC CRYPTATES: SALT SOLUBILIZATION AND ANION ACTIVATION[1]

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Lipophilic cryptands (I)-(III) bearing $C_{10}H_{21}$ side chains have been studied. [2.2.2, C_{10}] (I) forms complexes with various metal cations and solubilizes salts in solvents of low polarity to a greater extent than the parent system. Solvation of F^- by one $CHCl_3$ molecule has been observed and is necessary for KF dissolution in benzene. A study of the basicity of the *ter*-AmO^- anion in the presence of cryptate counterions gave $pK_a \geqslant 37$ for *ter*-AmOH, a value approaching the gas phase properties.

One of the original motivations of our work on cryptates[2] *rested on their* potential use for salt solubilization, anion activation and phase transfer catalysis. Solubilization of salts in organic media of low polarity and separation of ion pairs by ligands forming strong complexes with metal cations should produce very reactive anions. Such activation of the counter-anions is particularly attractive in view of the large number of organic reactions using reagents which contain alkali cations, or, to a lesser extent, alkaline-earth cations.

In a given medium, *anion activation will be stronger*, the larger the cation-anion distance imposed by the ligand. In order to achieve large cation-anion distances, the cation must be entirely wrapped up by a thick ligand so as to allow only weak interactions with the anion; in addition the anion will be very little solvated in media of low polarity, thus becoming very reactive.

Macrocyclic polyethers of the "crown" type have been used successfull for salt solubilization and activation (see for instance ref. 3-5). However, macrobicyclic ligands[6] form cation inclusion complexes, cryptates,[7] which are much more stable than the crown complexes[8] *and in which the cation is completely*

surrounded by the ligand and hidden inside the nearly spherical molecular cavity. In contrast direct cation anion contact is still possible in the crown complexes as shown for instance in crystal structures (see references in ref. 2). One may consider that complexation of K^+ (2.7 Å diameter) by the cryptand [2.2.2] leads to the formation of a very large spherical cation (about 10 Å diameter), a sort of "super-heavy" alkali metal cation (diameter of $Cs^+ \sim 3.3$ Å) interacting only weakly with anions or solvent molecules.

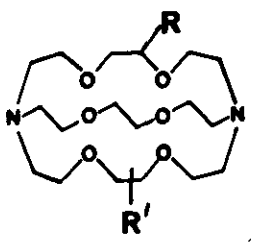
Thus cryptates appear to be ideally suited for anion activation and have been used for instance for producing highly basic species[9], for dissolving metals[10,11] and stabilizing alkali metal anions[12], for modifying the course of carbanion rearrangements[13], for ester formation[14], for initiating efficient anionic polymerization[15]. All these studies were conducted with the original cryptands which although easily soluble in organic solvents are also soluble in water[6] and probably not lipophilic enough for making optimal use of their complexing power. Indeed, the better the cation-anion separation by the ligand, the lower should be their solubility in low polarity solvents since stabilization by ion-pairing and aggregation is much reduced. Thus, solid-to-liquid or liquid-to-liquid phase transfer catalysis (PTC) also requires lipophilic cryptands as transfer agents in order to achieve the efficient extraction (and therefore catalysis) promised by the high stabilities of the complexes. Indeed, derivatives of the [2.2.2] cryptand bearing $n\text{-}C_{14}H_{29}$ and $n\text{-}C_{11}H_{23}$ side chains have recently been shown to be highly efficient catalysts in a number of two-phase reactions[16].

We have synthesized and investigated mainly the cryptand [2.2.2, C_{10}] (I); two other lipophilic cryptands are being studied: [2.2.2, $2C_{10}$] (II) and [2.2.1, C_{10}] (III)[17]. (I)-(III) are analogs of the parent systems [2.2.2] (IV) and [2.2.1] (V)[6].

SYNTHESIS

Cryptands (I)-(III) were obtained using the methods previously described for the preparation of the parent compounds [2.2.2], (IV), and [2.2.1] (V). The required lipophilic diacid (X) was obtained by the following reactions: epoxidation of 1-dodecene (permaleic acid in CH_2Cl_2, 0°, 24h.) gives the epoxide (VI) (bp 75°/0.1mm Hg; 75% yield) which on acid treatment (2% H_2SO_4 in water/dioxane 1/3 at reflux for 6h.) opens to the diol (VII) (mp 52°, bp 140°/0.3mm Hg; 82% yield); chloromethylation of (VII) (paraformaldehyde, HCl gas,

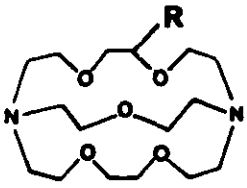
benzene/heptane 1/4, 10-12°, 2-3h.) gives the bis-chloromethylether (VIII) (oil; 83% yield) which is reacted with cyanide ($Cu_2(CN)_2$, 100°, 1h) forming the bis-nitrile (IX) (bp 272°/5.10^{-5} mm Hg; 50% yield); on hydrolysis (conc. HCl at reflux for 2.5 h.) (IX) gives the diacid (X) (mp 62°; 72% yield); treatment of (X) with oxalyl chloride (benzene, room temperature, 24h.) affords the bis-acid chloride (XI) (oil, crystalline at -25°; 98% yield; diamid: mp 90°).



(I) R = $C_{10}H_{21}$, R' = H

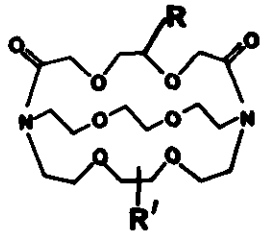
(II) R = R' = $C_{10}H_{21}$

(IV) R = R' = H



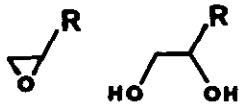
(III) R = $C_{10}H_{21}$

(V) R = H

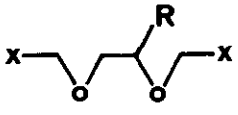


(XIII) R = $C_{10}H_{21}$, R' = H

(XVI) R = R' = $C_{10}H_{21}$



(VI) (VII) R = $C_{10}H_{21}$



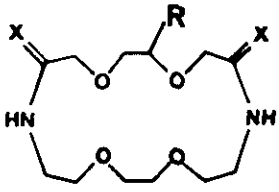
(VIII) X = Cl

(IX) X = CN

(X) X = COOH

(XI) X = COCl

R = $C_{10}H_{21}$



(XII) X = H_2, R = H

(XIV) X = O, R = $C_{10}H_{21}$

(XV) X = H_2, R = $C_{10}H_{21}$

Condensation of (XI) with the macrocyclic diamine (XII)[6] in high dilution conditions[6] gives the macrobicyclic diamide (XIII) (oil; 70% yield) which on reduction with diborane[6] gives the lipophilic cryptand [2.2.2, C_{10}], (I) (waxy crystals mp ∿ -5°; 70% yield). Similarly, (II) is accessible via (XIV)

(mp 55°), (XV) (oil) and (XVI) (oil). (XVI) and (II) are expected to be a mixture of isomers. Finally, (III) may be obtained in analogous fashion[17] from the corresponding bis-lactam resulting itself from the condensation of (XI) with the suitable macrocyclic diamine[6]. The structure of the compounds described follows from their synthesis and is in agreement with the spectral and analytical data.

PROPERTIES

Cation Complexation. Ligands (I)-(III) should display complexation properties similar to those of the parent systems (IV) and (V) and form cryptate type inclusion complexes[7,8]. (I) is soluble in all common organic solvents including pentane but forms milky mixtures with water. Cryptate formation is easily observed by ^{1}H (see figure 1) and ^{13}C NMR spectroscopy and occurs rapidly in such solvents as $CDCl_3$, CH_3CN for instance between KI, KBr, KCl, KF, $AgNO_3$ and (I). Stability constants in methanol have not yet been determined but are expected to be similar to those of (IV) and (V)[8].

Salt Solubilization.

With a non polar solvent like benzene the effect of the hydrocarbon chain becomes apparent. The complexes are prepared in acetonitrile which is then completely evaporated and their solubility is tested. The potassium cryptates of [2.2.2, C_{10}] with the following anions are soluble at > 0.1 mole/liter: picrate, NO_2^-, NO_3^-, SCN^-, NCO^-, $\underline{n}$-C_5H_{11}-COO^-, CN^-, I^-, Br^-, Cl^-. Of these only the cryptate with the very soft picrate anion is slightly soluble in heptane (about 10^{-4}M). The difference between benzene and heptane is striking; it is much more pronounced than one would expect on the basis of their dielectric constants (ε = 2.28 and 1.90 respectively) and points to comparatively better solvation by benzene probably because of its anisotropic polarisability. With [2.2.2], (IV), itself the solubilities are appreciably lower, for instance its KBr and KCl cryptates are not soluble in benzene.

Potassium fluoride deserves special mention because of its high lattice energy and of the very hard fluoride anion. When excess KF (dried by fusion under vacuum in a quartz tube) is added to [2.2.2, C_{10}] in acetonitrile (1 ml), complexation occurs. Filtration and evaporation of the solvent gives an oily residue which becomes cloudy in a few hours: decomplexation occurs, KF is deposited and the uncomplexed ligand is obtained. The same decomplexation occurs when heptane is added to the neat cryptate of (I) with $\underline{n}$-$C_5H_{11}COOK$.

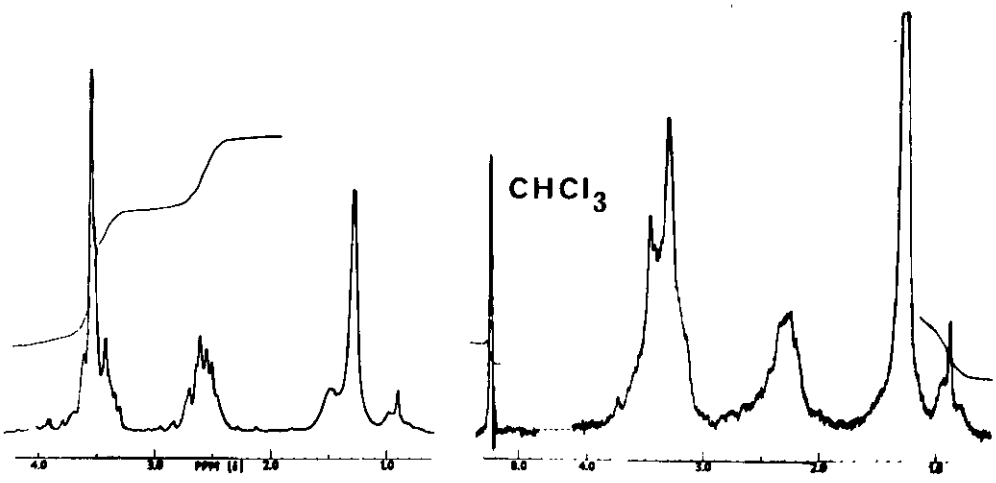


Figure 1. ^{1}H NMR spectra (60 MHz) of ligand (I), [2.2.2, C_{10}] in benzene-d_6 (left) and of its KF complex in benzene-d_6 containing about 1 equivalent of $CHCl_3$ (right).

Thus, despite the very high stability of the cryptates[8], the salts of the hardest anions like F^- (the same probably holds for OH^-) are not appreciably dissolved in benzene (nor of course in heptane) in the exclusion of any anion solvating species. The effect of the latter is shown in the following experiment. The $[K^+ \subset (2.2.2, C_{10})]\ F^-$ cryptate is prepared in chloroform (in a dry box under nitrogen); the solution is transferred into an NMR tube sealed on a vacuum line and the solvent is pumped off (5 days at 10^{-5}mm Hg). Dry benzene-d_6 is added and the NMR tube is sealed off. The KF cryptate is found to dissolve in the benzene, but the proton NMR spectrum shows that, despite the prolonged pumping, about one chloroform molecule is left per cryptate (within 10%) and the $CHCl_3$ resonance occurs at 8.25 ppm i.e. 2 ppm downfield from its normal position in benzene solution (6.25 ppm) (figure 1). This indicates solvation of each fluoride anion by one chloroform molecule via strong $F^-..HCCl_3$ hydrogen bonding*. Attempts to remove the remaining chloroform lead to decomplexation.

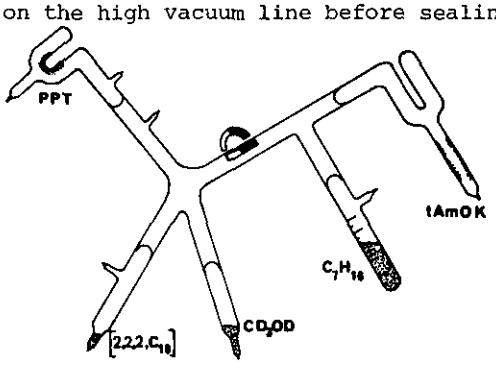
* Hydrogen bonding to triethylamine in cyclohexane gives a maximum shift of about 1.6 ppm[18].

These experiments strongly suggest that, despite their high complexing power and lipophilicity, even cryptands like (I) do not allow stoichiometric dissolution of KF in benzene; thus, in PTC experiments with KF[4,16], water molecules are probably extracted into the organic phase.

Basicity of the ter-Amylate Anion.

Since cryptates of ligands like (I) minimize cation anion interactions and solubilize suitable salts in organic solvents which do not solvate appreciably the anions, one may hope that such ligands allow to approach gas phase properties in solution. Experiments were conducted to determine the basicity of a tertiary alkoxide ion associated with a cryptate counterion in a medium of low polarity. It has already been shown that, whereas a solution of *ter*-AmOK in benzene does not ionize Ph_3CH or Ph_2CH_2, addition of [2.2.2] leads to immediate formation of the colored Ph_3C^- and Ph_2CH^- anions[9]. Thus the pK_a of *ter*-AmOH in these conditions is > 33.4 on Streitwieser's scale[19]. The present experiments made use of *ter*-AmOK, [2.2.2, C_{10}], heptane and *para*-phenyl-toluene (PPT) as pK_a indicator (with a pK_a of 38.7[19]). All operations were conducted under high vacuum (10^{-5}mm Hg) in a sealed apparatus featuring break-seals (figure 2), with materials purified on the high vacuum line before sealing off the apparatus.

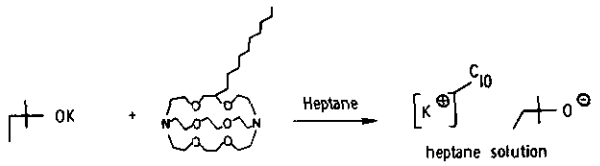
Figure 2

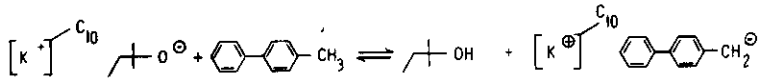


In this way reagents could be mixed without any external contact by breaking the seals in the desired order. The heptane is first condensed on the *ter*-amylate which dissolves entirely and the solution is then poured onto the PPT sample. No coloration is observed. This solution is then poured onto the [2.2.2, C_{10}] sample. Complexation of K^+ is expected to be very fast. No colour is obtained at this stage. When the heptane is then almost entirely taken off by condensation in one of the branches, the red color of the anion of PPT is observed in the oily residue; it is only stable for about 20 min. at about 0°.

The anion is destroyed with the methanol-d_4 sample, the apparatus is opened, the PPT isolated and analyzed by mass spectroscopy. About 10% incorporation of one deuterium atom is found. Since it is not known how much heptane was left at the moment of the quenching by methanol, a calculation assuming no heptane left (maximum base concentration) yields a lower limit of the pK_a. The result is $pK_a \geqslant 37$ for the *ter*-AmOH in the equilibrium shown in Figure 3 and in the present experimental conditions. Since the gas phase acidities are in the order[20]: methanol < toluene < ethanol < *i*-propanol < *ter*-butanol and the pK_a of toluene is 40.9 on Streitwieser's scale[19], the present pK_a value $\geqslant 37$ for *ter*-AmOH must indeed approach the gas phase value.

Figure 3





CONCLUSION

The results described corroborate the underlying ideas about solubilization and anion activation discussed in the introduction. Some reactions of the anions have been observed but a more extensive study in PTC conditions has been performed[16]. Extension towards even thicker and more lipophilic cryptands may be of interest. Both mechanistic studies (reactivity, regio-selectivity, stereo-selectivity of the reactions of contact ion pairs or cryptand separated ions) and synthetically useful developments may be envisaged, for instance by activating other reagents (e.g. BuLi with [2.1.1, C_{10}] etc.). In another line, [2.2.2, C_{10}] (I) and [2.2.1, C_{10}] (III) have been used as carriers for selective cation transport through membranes[21]. Finally, formation of micellar systems controlled by cation complexation, and incorporation of such cryptands into bilayer membranes, may be considered.

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