Complexes of Crown Ethers and Glymes with Difluorenylbarium

U. Takaki and J. Smid*

Contribution from the Chemistry Department, College of Environmental Science and Forestry, State University of New York, Syracuse, New York 13210. Received August 20, 1973

Abstract: Titrations of difluorenylbarium ($Ba^{2+}, Fl_2{}^{2-}$) with polyethylene glycol dimethyl ethers (glymes) and with macrocyclic polyethers (crown ethers) were carried out in THF at 25° under vacuum to determine the stoichiometries and structures of the resulting ion pair–glyme and –crown ether complexes. With mono- and dibenzo-18-crown-6 as well as with glyme-7 and glyme-9, 1:1 complexes are formed with difluorenylbarium. The optical spectra demonstrate that the species are mixed tight–loose ion pairs of the type Fl^-, Ba^{2+}, crown, Fl^-. With monobenzo-15-crown-5 a 2:1 crown–ion pair complex is formed (Fl^-, crown, Ba^{2+}, crown, Fl^-), the spectrum of which is identical with that of a fully separated ion pair. The formation constant for the latter complex is $1.3 \times 10^8 \ M^{-2}$. Glyme-23 also complexes with the barium salt to a fully separated ion pair and so does poly(vinylbenzo-15-crown-5). The polymer forms 2:1 crown–cation complexes with difluorenylbarium, while poly(vinylbenzo-18-crown-6) forms 1:1 complexes, although the ratio crown to cation for this system does not reach 1.0 due to electrostatic repulsion.

Numerous techniques have been applied in the past decade to study structures and reactivities of ion pairs of alkali carbanion and radical anion salts and their solvation complexes.[1] Information on organic ions associated with alkaline earth cations is far less abundant. The behavior of these ion pairs should be especially interesting since ion pair separation to form loose ion pairs may occur by a stepwise process.

In a recent communication[2] we reported evidence for such a stepwise formation of loose ion pairs from the tight ion pairs of difluorenylstrontium on cooling a tetrahydrofuran (THF) solution of this carbanion salt. Spectrophotometric measurements revealed the formation of mixed tight–loose ion pairs, i.e.

$$Fl^-, Sr^{2+}, Fl^- \rightleftarrows Fl^- || Sr^{2+}, Fl^- \rightleftarrows Fl^- || Sr^{2+} || Fl^-$$
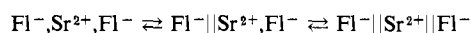
where the Fl^- denotes a fluorenyl carbanion and the sign $||$ refers to one or more solvent molecules or a cation complexing agent. Earlier work[3] with difluorenylbarium in THF demonstrated that the tight ion pair of this salt forms a 1:1 complex with the crown ether dibenzo-18-crown-6. The optical spectrum of this complex leaves little doubt that again a mixed tight–loose ion pair is formed of the type Fl^-, Ba^{2+}, crown, Fl^-.

In this paper we report the results of spectrophotometric studies of difluorenylbarium with crown ethers and with a few polymers endowed with crown ethers as pendent groups. These macrocyclic polyethers have recently received considerable attention because of their ability to bind alkali and alkaline earth cations and their subsequent use in enhancing the reactivity of organoalkali reagents and in promoting ion transport across biological membranes.[4] Depending on the size of the polyether cavity relative to that of the cation, one or two crown molecules complex to the ion pair of difluorenylbarium. A few experiments with the linear polyethylene glycol dimethyl ethers (glymes) are also included, showing that in these systems the structure of the resulting ion pair–glyme complex depends on the chain length of the glyme.

Experimental Section

Difluorenylbarium. To a 500-ml Pyrex flask was sealed a quartz finger of about 5 cm in length and 15 mm in diameter. A 2-cm long stainless steel cup of 12-mm diameter containing freshly cut barium metal was placed inside the finger. Also attached to the flask were an evacuated ampoule with break-seal containing purified 1,1-diphenylethylene, a similar ampoule containing recrystallized fluorene, and an optical cell of 2-mm pathlength provided with a quartz spacer. The entire apparatus was evacuated and baked out on a vacuum line. The barium was then vaporized by gently heating the quartz finger, producing a clean barium mirror on the surface of the 500-ml bulb. About 200 ml of pure THF was distilled from a storage flask onto the cooled barium mirror, and the entire apparatus was sealed off the vacuum rack. The 1,1-diphenylethylene was added to the THF and the solution shaken on the mirror for a prolonged period of time (up to 3 weeks). The slowly developing red dianion of 1,1-diphenylethylene eventually reached a concentration of about $10^{-2} \ M$. The reaction was then stopped and a slight excess of fluorene added, producing rapidly and quantitatively difluorenylbarium (the reaction is monitored by observing the disappearance of the 447-nm absorption peak of the barium dicarbanion salt). The orange solution was removed from the mirror and concentrated, and difluorenylbarium precipitated by cooling. The salt was filtered off and recrystallized from pure THF under vacuum. It was obtained in orange needle like crystals free of fluorene and of 1,1-diphenylethylene.

Crown Ethers and Glymes. The preparation of the crown compounds dimethyldibenzo-18-crown-6, methylbenzo-18-crown-6, and methylbenzo-15-crown-5 has been described elsewhere.[5,6] The synthesis of the 4'-vinyl monomers of benzo-15-crown-5 and of benzo-18-crown-6, and their subsequent conversion to high molecular weight polymers, have also been discussed.[7] The number average molecular weight of the two polymers was 110,000. Tetraethylene glycol dimethyl ether or glyme-5 (Aldrich) and hexaethylene glycol dimethyl ether or glyme-7 (Schuchardt) were puri-

(1) For a review on several aspects of these studies, see M. Szwarc, Ed., "Ions and Ion Pairs in Organic Reactions," Vol. 1, Wiley-Interscience, New York, N. Y., 1972; J. Smid, *Angew. Chem., Int. Ed. Engl.*, **11**, 112 (1972).

(2) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **94**, 9240 (1972).

(3) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **91**, 4580 (1969).

(4) For a general discussion of these compounds, see C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972).

(5) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 7017 (1967); C. J. Pedersen, *ibid.*, **92**, 386 (1970).

(6) U. Takaki, T. E. Hogen-Esch, and J. Smid, *J. Amer. Chem. Soc.*, **93**, 6760 (1971).

(7) S. Kopolow, T. E. Hogen-Esch, and J. Smid, *Macromolecules*, **6**, 133 (1973).

fied on sodium–potassium alloy.[8] Octaethylene glycol dimethyl ether (glyme-9) was prepared by reacting sodium methoxide with a large excess of methoxytriethylene glycol with removal of the methanol formed. The resulting sodium methoxyglycolate was then reacted with dichloroethyl ether in a 2:1 molar ratio. The product $CH_3(OCH_2CH_2)_8OCH_3$ was purified by fractional distillation and distilled twice under vacuum from calcium hydride. The purity of the compound was checked by tlc and nmr.

Glyme-23 was synthesized by methylating Union Carbide carbowax 1000 (containing on the average 23 oxygen atoms per molecule). The carbowax (5 g) was dissolved in 100 cm³ of THF and converted to the sodium salt by adding sodium naphthalene in THF until the green color of the radical anion solution persisted. The very viscous solution was then treated with an excess of methyl iodide and the reaction mixture stirred overnight. The viscosity of the solution slowly diminished and sodium iodide precipitated out. The mixture was filtered and the solvent evaporated. The entire procedure up to this point was carried out under vacuum. The crude product was purified on a column of neutral alumina, activity 1, with toluene–chloroform mixtures as the eluting solvent. The product was isolated from the 1:1 mixture as a wax like material after solvent evaporation. It was further purified by recrystallization from a 1:1 mixture of toluene and n-hexane. The white solid, after drying, has a melting point of 35.5–36.5°, the ¹H nmr spectrum showing the correct ratio of methyl to methylene protons.

Titrations. Stoichiometries of the crown and glyme complexes with difluorenylbarium, and the respective complex formation constants, were determined by titrating under vacuum a THF solution of the complexing agent with a THF solution containing difluorenylbarium. The latter solution, the concentration of which was determined spectrophotometrically in an optical cell attached to the flask containing the salt, was added in small aliquots. After each addition the absorbance was recorded in a Cary 14 spectrophotometer by means of optical cells attached to the flask containing the solution of the complexing agent. The two solutions were separated from one another by a shut-off valve consisting of a glass enclosed magnet which can be operated by an external magnet. No regular stopcocks are used, and the titration of the moisture and oxygen sensitive systems can be performed with a better than five % accuracy down to carbanion concentrations of the order of 10^{-5} M. Absorption coefficients of some of the species were obtained in a similar way by replacing the complexing agent with pure 4-methylcathecol, which decolorizes the carbanion by protonation. A drawing of the apparatus and a description of the titration procedure have been published elsewhere.[9]

Results

Fluorenyl alkali salts can be obtained by stirring the hydrocarbon in THF directly on the respective metal mirrors,[10,11] but the reaction with barium is very slow. For this reason, the barium dianion of 1,1-diphenylethylene was prepared first,[12] and even this reaction is comparatively slow. The red dianion (λ_m 447 nm) reacts quantitatively and rapidly with fluorene to form difluorenylbarium. Alkaline earth salts of fluorenyl have also been prepared directly by reacting fluorene with the metal dissolved in liquid ammonia.[13] After completion of the reaction the ammonia is evaporated and replaced by THF or another solvent. The spectra of the barium salts prepared by the two methods are identical, the absorption maximum in THF being 347 nm (Figure 1). A shoulder at 373 nm may indicate the presence of a small fraction (about 0.05) of loose ion pairs (probably a mixed tight–loose pair of the type Fl⁻,Ba²⁺‖Fl⁻), and it increases on lowering the temperature. However, even at −70° the fraction is not

(8) K. H. Wong, L. L. Chan, and J. Smid, *J. Amer. Chem. Soc.*, **92**, 1955 (1970).

(9) L. Ambroz, K. H. Wong, and J. Smid, *Anal. Chem.*, **44**, 872 (1972).

(10) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307 (1966).

(11) T. Ellingsen and J. Smid, *J. Phys. Chem.*, **73**, 2712 (1969).

(12) J. C. Favier, M. Fontanille, and P. Sigwalt, *Bull. Soc. Chim. Fr.*, 526 (1971).

(13) J. P. Pascault and J. Golé, *J. Chim. Phys.*, **68**, 449 (1971).
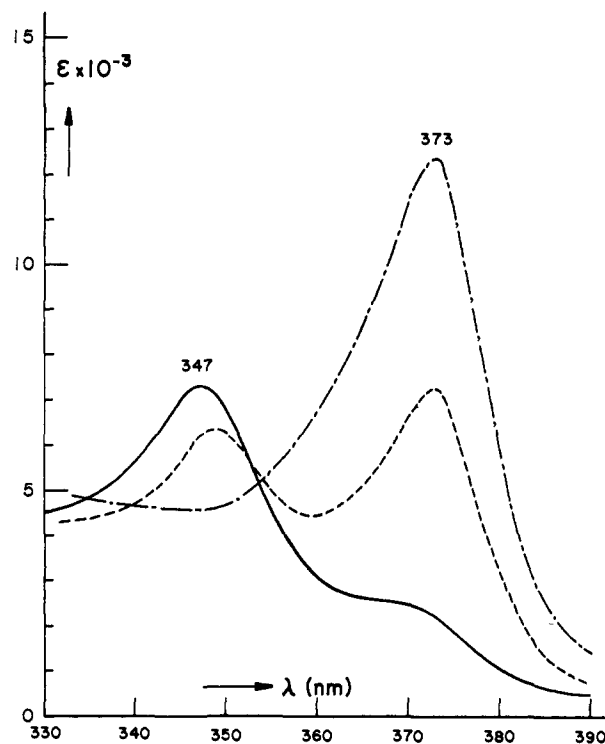
Figure 1. (—) Optical spectrum of difluorenylbarium in tetrahydrofuran at 25°; (- - -) 1:1 complex of 4'-methylbenzo-18-crown-6 and Ba^{2+},Fl_2^{2-} (Fl⁻, Ba^{2+}, crown, Fl⁻); (- · -) 2:1 complex of 4'-methylbenzo-15-crown-5 and Ba^{2+}, Fl_2^{2-} (Fl⁻, crown, Ba^{2+}, crown, Fl⁻).

much higher than 0.1. Apparently the enthalpy of separated ion pair formation in THF is only slightly exothermic for Ba^{2+},Fl_2^{2-}.

To further check the purity of the salt the ratio of barium to fluorenyl was determined by terminating a carbanion solution of known volume and optical density with a drop of water. The amount of fluorene formed was measured spectrophotometrically at λ_m 301 nm (ϵ 9250) while barium hydroxide was titrated with aqueous HCl after evaporation of the THF. The ratio Ba^{2+} to fluorenyl was found to be 1.14:2.00. The barium content is a little higher than it should be, possibly because of inaccuracy in the titration of the low $Ba(OH)_2$ concentration.

The absorption coefficient, ϵ_m, of the fluorenyl anion in the tight ion pair of difluorenylbarium in THF at λ_m 347 nm was found to be 7300 (if corrected for the small fraction of loose ion pairs, the ϵ_m of the fluorenyl "pure" tight ion pair in THF would be 7700). This compares with a value of 11,000–12,000 for the tight ion pairs of the alkali fluorenyl salts in THF.[9,10] The much lower value obtained for the barium salt may be due to hypochroism, a phenomenon observed in polynucleotides,[14] where the absorbance of the purine and pyrimidine residues is lowered when helix formation leads to parallel stacking of the base units. A comparable situation may exist in a salt such as difluorenylbarium where the barium ion is sandwiched in between two nearly parallel oriented fluorenyl rings. An increase in the distance between the two rings is expected to enhance the absorption coefficient. This is found when crown ethers are complexed to the barium salt.

(14) A. Rich and I. Tinoco, Jr., *J. Amer. Chem. Soc.*, **82**, 6409 (1960); I. Tinoco, *ibid.*, **82**, 4785 (1960).
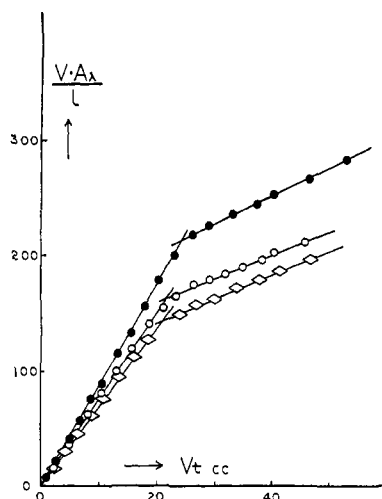
Figure 2. Titration plots VA_λ/l vs. V_t for difluorenylbarium in THF at 25° with (●) 4'-methylbenzo-18-crown-6, (○) glyme-9 (octaethylene glycol dimethyl ether), and (◇) glyme-7 (hexaethylene glycol dimethyl ether).

The tight ion pair is converted to a crown separated ion pair, and the distance between the two fluorenyl moieties is considerably enlarged. For the complexes of monobenzo-15-crown-5 and poly(vinylbenzo-15-crown-5) with difluorenylbarium the respective absorption coefficients are 12,400 and 13,700. For a similar complex with fluorenylpotassium, ϵ_m is equal to 14,300.[9] Although the replacement of solvent molecules around an alkali ion pair by a glyme or a crown molecule also increases the absorption coefficient as a result of changes in the vibrational energy levels (ϵ_m is higher by about 20% as compared to the tight alkali fluorenyl ion pair), the increase for difluorenylbarium amounts to almost a doubling of ϵ_m (see also Figure 1).

Titrations. The optical spectrum of complexes of difluorenylbarium with crown ethers or glymes depends on the structure of the complexing agent. Addition of monobenzo-18-crown-6 (and also of dibenzo-18-crown-6, glyme-7 and glyme-9) to difluorenylbarium in THF yields a spectrum with maxima at 349 and 373 nm (see Figure 1), and as long as the complexing agent is in excess the shape of the spectrum remains unchanged. On the other hand, addition of monobenzo-15-crown-5 produces only one absorption peak in the 350–400-nm region of the difluorenylbarium spectrum, i.e., at 373 nm. A similar spectrum is found with poly(vinylbenzo-15-crown-5) and with glyme-23.

To further establish the structure of the complexes, the ratio of crown ether to difluorenylbarium in the complex was determined by carefully titrating a THF solution of crown ether of volume V_0 with a solution of difluorenylbarium of concentration C_t (concentration of fluorenyl carbanions). After each addition of the carbanion solution the absorbance A_λ at 373 nm (and/or that at the tight ion pair maximum) was measured in a cell of optical length l. If V_t is the amount of titrant added and $V = V_0 + V_t$, it can be shown[9] that for a high complexation constant a plot of the product VA_λ/l vs. V_t is given by two straight lines.

$$VA_\lambda/l = C_t V_t \epsilon_c$$

and

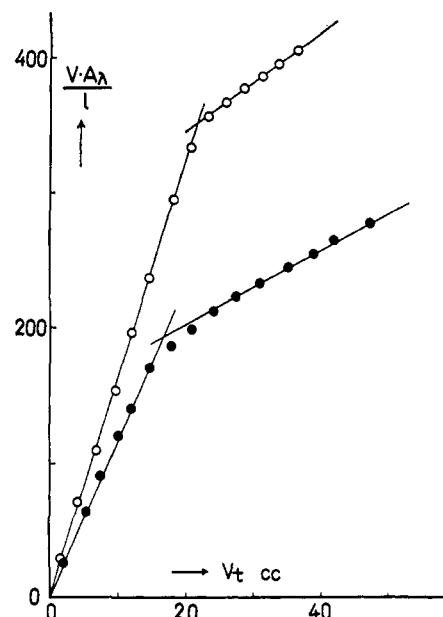$$VA_\lambda/l = (\epsilon_c - \epsilon_t)C_t V_t^* + C_t V_t \epsilon_t$$

Figure 3. Titration plots VA_λ/l vs. V_t for difluorenylbarium in THF at 25° with (○) poly(vinylbenzo-15-crown-5) and (●) poly(vinylbenzo-18-crown-6).

The two lines intersect at V_t^* which represents the amount of difluorenylbarium needed to complex all the crown ether. The quantities ϵ_c and ϵ_t are the absorption coefficients of the fluorenyl carbanion in the complex salt and in that of the tight ion pair, respectively, at 373 nm. The relationship, of course, also holds at any other wavelength if the appropriate absorption coefficients are used. From the value of V_t^*, the stoichiometric ratio of complexing agent to barium in the complex can be calculated while the slopes of the respective lines yield values for ϵ_c and ϵ_t.

A few such plots are depicted in Figures 2 and 3. In most of the systems studied the breaking point is sharp under the prevailing experimental conditions. No clear break was found for glyme-5, while precipitation occurred with 4'-methylbenzo-15-crown-5 before an equimolar amount of salt could be added.

In the latter system formation of a 2:1 crown–barium complex was suspected since only the loose ion pair peak at 373 nm was found as long as [15C5] > 2[Ba²⁺,-Fl₂²⁻]. The formation constant of this complex was determined from the overlap of the spectra of the tight and crown-separated ion pair at different concentrations of the reactants. In the absence of crown a small fraction (estimated from the spectrum to be 0.05) of loose ion pairs Fl,Ba²⁺||Fl⁻ is present in a THF solution of difluorenylbarium. The benzo-15-crown-5 converts the tight ion pair to the fully separated pair, and it is assumed that two crown molecules are involved.

$$\text{Fl}^-,\text{Ba}^{2+},\text{Fl}^- + 2(\text{crown}) \rightleftharpoons \text{Fl}^-,\text{crown},\text{Ba}^{2+},\text{crown},\text{Fl}^- \qquad K$$

If $\alpha = [\text{Fl}^-,\text{Ba}^{2+}||\text{Fl}^-]/\text{tight ion pairs}$, then the experimentally observed ratio R of loose (373 nm) over tight (347 nm) ion pairs is given by the expression

$$R = \alpha + (1 - \alpha)K[\text{crown}]^2$$

where [crown] = [crown]₀ − [loose ion pairs] + α[tight ion pairs] (the concentration of ion pairs is expressed in concentration of fluorenyl moieties). A plot of R

vs. [crown]^2 is shown in Figure 4, and the linear relationship confirms the correctness of the assumption that two benzo-15-crown-5 molecules are complexed to Ba^{2+}. The intercept α was found to be 0.07 and the formation constant K is 1.3×10^8 M^{-2}.

The composition of the respective crown and glyme complexes is given in Table I. For the two polymers

Table I. Composition of Crown and Glyme Complexes of Difluorenylbarium in THF at 25°

Complexing ether	Ratio Ether/ Ba^{2+},Fl$_2^{2-}$ in complex	Abs(373)/ Abs(347)
THF	0	0.22
Dimethyldibenzo-18-crown-6	1.00	1.18
4-Methylbenzo-18-crown-6	0.98	1.18
4-Methylbenzo-15-crown-5^a	2.0	2.76
Poly(vinylbenzo-18-crown-6)^b	1.4	1.90
Poly(vinylbenzo-15-crown-5)^b	2.2	1.90
Glyme-5^c	2.0	3.80
Glyme-7	1.04	1.16
Glyme-9	1.01	1.37
Glyme-23^d		2.90

^{a} Complex precipitates above 10^{-3} M. Below this concentration it partially dissociates in solution. The ratio of 2.0 is found from a study of the equilibrium BaFl$_2$ + n(crown) $\rightleftarrows$ BaFl$_2$(crown)$_n$. ^{b} Ratios refer to concentration of crown units over molar concentration of difluorenylbarium at V_t^*. ^{c} Solution contains equal volumes of THF and glyme-5. At a glyme-5 concentration of 2.10^{-3} M, the value for Abs(373)/Abs(347) is equal to 0.62. The ratio of 2.0 was derived from a study of the equilibrium BaFl$_2$ + n(glyme) $\rightleftarrows$ BaFl$_2$(glyme)$_n$. ^{d} Solution is turbid under the condition of the experiment ($\approx 10^{-4}$ M salt).

the ratios of crown to barium are expressed as concentration of crown units over the molar concentration of difluorenylbarium.

To check the reliability of the titration procedure the ratio of crown-separated to tight ion pairs was also determined directly from the optical spectrum of mixtures of dimethyldibenzo-18-crown-6 and difluorenylbarium. The spectrum can be interpreted as the superposition of the spectrum of a tight ion pair (ϵ_m 347 = 7700, ϵ 373 = 1630) and that of a loose ion pair (*e.g.*, the complex of Ba^{2+},Fl$_2^{2-}$ and 15C5, ϵ_m 373 = 12,400 and ϵ 347 = 4500). The calculations show that as long as [crown] > [Ba^{2+},Fl$_2^{2-}$] the optical spectrum does not change, and the ratio of crown-separated to tight ion pairs in this system is equal to 0.97 ± 0.01. This confirms the titration results, *i.e.*, the 1:1 complex formation of this crown ether with Ba^{2+},Fl$_2^{2-}$.

Although solutions of Ba^{2+},Fl$_2^{2-}$ in THF as high as 5.10^{-2} M can be prepared, the solubility of the crown and glyme complexes is much smaller (10^{-3}–10^{-2} M). Frequently, crown ethers and glymes will vastly improve the solubility of salts in media of low polarity.[5,15] Apparently, there are many exceptions especially when complex formation leads to a separated ion pair and, consequently, enlargement of the dipole moment of the ionic species. This enhances the probability of aggregation, as was also noted for crown-separated ion pairs of alkali fluorenyl salts.[16] Special care must be taken when polymers are used, as precipitation can already occur at Ba^{2+},Fl$_2^{2-}$ concentrations as low as 5.10^{-4} M.

(15) D. J. Sam and H. E. Simmons, *J. Amer. Chem. Soc.*, **94**, 4024 (1972).
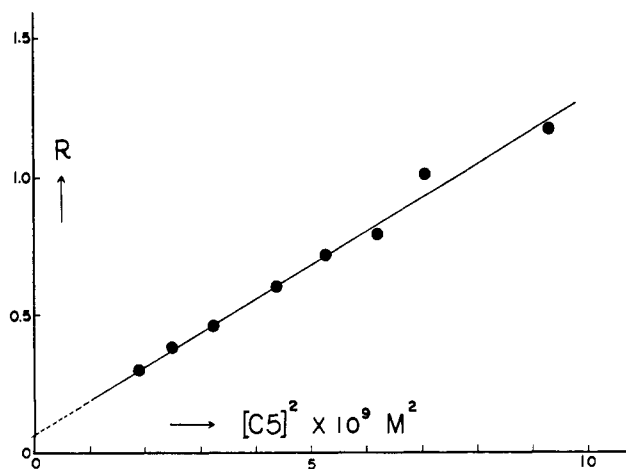(16) U. Takaki and J. Smid, *J. Phys. Chem.*, **76**, 2152 (1972).

Figure 4. Plot of ratio R (= [loose ion pairs]/[tight ion pairs]) *vs.* square of crown concentration for the system difluorenylbarium and 4'-methylbenzo-15-crown-5 in THF at 25°.

However, even under these conditions the fraction of free fluorenyl carbanions resulting from dissociation is small. The free ion dissociation constant for the tight ion pair in THF at 20° is only 5.3×10^{-9} M,[17] while that of the crown complex with dibenzo-18-crown-6 is 5.4×10^{-7} M.[17]

Discussion

Table I shows that the ratio Abs(373)/Abs(347) of the two ion pair maxima in the spectra of certain 1:1 crown and glyme complexes of difluorenylbarium is constant ($\sim$1.2) under conditions where [crown] or [glyme] > [Ba^{2+},Fl$_2^{2-}$]. This suggests the presence of mixed ion pairs of the type Fl$^-$,Ba^{2+}, crown,Fl$^-$ or Fl$^-$,Ba^{2+},glyme,Fl$^-$. Such an ion pair complex represents energetically a more favorable structure than one in which the Ba^{2+} ion is centered in the cavity of the crown ether, with the two fluorenyl rings at approximately equal distances from the cation. In the latter case only one absorption peak is expected in the optical spectrum at around 360 nm. It is questionable whether such a structure would be possible in view of the relative sizes of the Ba^{2+} cation and the 18C6 cavity. The diameter of the polyether ring has been estimated[4] to be 2.6–3.2 Å (the lower value is based on CPK models), while the Pauling diameter for Ba^{2+} is 2.70 Å. However, recent calculations[18] have yielded a diameter for Ba^{2+} of 2.98 Å. Therefore, if the lower estimate for the 18C6 ring is correct, the Ba^{2+} ion would be too large to pass through the 18C6 ring, and a mixed tight–loose ion pair in that case is more likely. Dalley, *et al.*, reported an X-ray analysis of the crystalline complex of Ba(NCS)$_2$ with dicyclohexyl-18-crown-6, showing that the Ba^{2+} ion is coordinated to the six oxygen atoms of the nearly planar polyether ring and to the N atoms of the two NCS ions.[19] The reported Ba–O distances of 2.77–2.89 Å suggest that also in the solid complex the Ba^{2+} ion is located above the crown ring.

The mixed tight–loose ion pair represents a combination of a crown-separated and a crown-complexed tight ion pair. Both species exist in mixtures of crown ethers

(17) T. E. Hogen-Esch and J. Smid, unpublished results from this laboratory.
(18) M. F. C. Ladd, *Theor. Chim. Acta*, **12**, 333 (1968).
(19) N. K. Dalley, D. E. Smith, R. M. Izatt, and J. J. Christensen, *Chem. Commun.*, 90 (1972).

or glymes with alkali carbanion pairs in THF,[6,8] e.g., in mixtures of monobenzo-15-crown-5 and fluorenyl sodium or of glyme-6 or glyme-7 with fluorenylpotassium.

Glyme-7 and -9 also form mixed ion pairs with difluorenylbarium as indicated from the values for the ratio Abs(373)/Abs(347) (see Table I). Apparently, not enough binding sites can be provided for in these 1:1 complexes by either glyme-7 or -9 to compensate for the loss in electrostatic energy and conformational entropy on formation of a fully glyme separated ion pair, although the absorbance ratio of 1.37 found for glyme-9 suggests the presence of a small fraction of such ion pairs. The formation constants of the glyme-7 and glyme-9 ion pair complexes with fluorenylbarium were found to be 10^5 M^{-1} or higher, which is at least a factor of 100 larger than the formation constant for the glyme-7 complex of fluorenylpotassium.[8] Also, there is no evidence that under our experimental conditions a second glyme molecule becomes associated with the barium salt. Earlier work showed that even in pure glyme-4 and glyme-6 the mixed 1:1 tight–loose ion pair complex is the only species present at 25°.[3]

It is, therefore, interesting that both monobenzo-15-crown-5 and glyme-5 do not form a mixed ion pair but a fully separated fluorenylbarium ion pair containing two crown or glyme molecules, respectively. The 2:1 crown–cation complexes are often formed when the cation diameter is larger than that of the crown cavity. Two to one benzo-15-crown-5 or glyme-5 complexes also exist with fluorenylpotassium[6,8] and other potassium salts.[4,7] The complex formation constant of $Ba^{2+},Fl_2{}^{2-}$ with glyme-5 was found to be approximately 7×10^4 M^{-2}, as compared to a value of 1.3×10^8 M^{-2} found with monobenzo-15-crown-5.

A very stable complex of barium tetraphenylboron and the nonylphenoxy ether of polyethylene glycol containing 12 ethylene oxide units has recently been made.[20] The neutral carrier can be used as an exchanger in a barium ion-selective electrode with selectivity ratios greater than 10,000 to 1 for Ba^{2+} over Ca^{2+}, Mg^{2+}, and other cations. Complexes containing 12 ethylene oxide units per mole of $Ba(BPh_4)_2$ were also reported for polyethylene glycols of higher chain length,[21] while a composition of 10.4 was found for polyethylene glycols of molecular weights between 600 and 4000.[22] The observation that monobenzo-15-crown-5 and glyme-5 form a stable 2:1 complex with difluorenylbarium suggests that a molecule such as glyme-10 may contain sufficient binding sites to form a fully separated 1:1 ion pair complex. Such an ion pair is obtained when difluorenylbarium is complexed with glyme-23 (Table I), and it is possible that two $Ba^{2+},Fl_2{}^{2-}$ molecules are complexed to this glyme. A 1:2 complex was found to exist in a THF solution of glyme-23 and fluorenyl sodium.[23]

Ligands which can envelope a barium ion to form a completed solvation shell with minimal conformational changes should be very effective in forming fully separated ion pairs. Not surprisingly, a 1:1 mixture of difluorenylbarium and $N-(CH_2CH_2OCH_2CH_2OCH_2-CH_2)_3-N$ in THF forms a complex (generally referred to as cryptates, see ref 24), the spectrum of which reveals one ion pair maximum at 373 nm, even at concentrations below 10^{-4} M. Some of the interesting crown ethers recently synthesized by Cram, et al.,[25] should also be very effective in this respect.

Results obtained for the polymeric crown ethers (Table I) are consistent with the findings reported for alkali cations.[7] The existence of 2:1 complexes of monobenzo-15-crown-5 with Ba^{2+} implies that the polymer containing this crown structure as pendent group (P15C5) should bind Ba^{2+} more effectively. This is confirmed by the sharpness of the titration plot (Figure 3) as compared to that of the monomeric analog (the plot of which exhibits a curvature under similar experimental conditions). The polymer P15C5 interacts with $Ba^{2+},Fl_2{}^{2-}$ to form fully separated ion pairs (as indicated by the value of 2.8 for the ratio Abs(373)/Abs(347)), and at least two crown units are involved in complexing the ion pair. In this respect, the barium salt again resembles the potassium salt, as the latter also forms a 2:1 complex with P15C5. In both cases the ratio 15C5/cation is slightly higher than two. This is not unreasonable as the most probable ion distribution on such a polymer chain is one in which 13% of the crown units become isolated.[26] While this strictly applies only to an irreversible system, complete saturation in our case constitutes additional loss of entropy. Also, the complex formation constant is likely to decrease with increasing cation population along the chain as a result of electrostatic repulsion. This becomes an even bigger problem when the cations form 1:1 complexes with the polymer, e.g., with poly-(vinylbenzo-18-crown-6) (P18C6), especially when the cations are divalent. For fluorenylpotassium the minimum crown to cation ratio in P18C6 was found to be 1.2,[23] while for $Ba^{2+},Fl_2{}^{2-}$ the ratio did not go below 1.4 (Table I). The spectrum of the $P18C6-Ba^{2+},Fl_2{}^{2-}$ complex is in between that of a fully separated ion pair and that of a mixed tight–loose ion pair. Apparently, the latter type of ion pair, formed with monomeric 18C6, is more difficult to form in P18C6 as adjacent 18C6 moieties tend to prevent a close approach of the fluorenyl anion to the Ba^{2+} cation.

The complex formation constants of $Ba^{2+},Fl_2{}^{2-}$ with P18C6 and P15C5 in THF were too large to measure under our experimental conditions (concentrations of reagents $\sim 10^{-4}$ M). However, competition experiments demonstrate that in a mixture of P15C5 with Ba^{2+} and K^+ ions the Ba^{2+} ions are preferentially bound. Addition of $Ba^{2+},Fl_2{}^{2-}$ to a mixture of $P15C5-Fl^-,K^+$ (λ 373 nm, ratio 15C5/K^+ > 2) produces a spectrum in which the tight ion pair maximum of the barium salt (347 nm) is absent. Instead, the 362-nm maximum of the Fl^-,K^+ tight ion pair is formed, implying that barium ions have replaced the K^+ ions on the polymer chain.

We are presently preparing copolymers of styrene and vinylbenzo crown ethers containing varying amounts of crown units in the chain. It is anticipated that an increased average distance between adjacent crown units will decrease repulsion between cations as the polymer

(20) R. J. Levins, Anal. Chem., 43, 1045 (1971).
(21) T. Uno and K. Miyajima, Chem. Pharm. Bull., 11, 75 (1963).
(22) R. J. Levins and R. M. Ikeda, Anal. Chem., 37, 671 (1965).
(23) Z. Machacek and J. Smid, unpublished results from this laboratory.

(24) B. Dietrich, J. M. Lehn, and J. P. Sauvage, Tetrahedron Lett., 2889 (1969).
(25) R. C. Helgeson, J. M. Timko, and D. J. Cram, J. Amer. Chem. Soc., 95, 3025 (1973).
(26) P. J. Flory, J. Amer. Chem. Soc., 61, 1518 (1939).

chain becomes saturated with cations, and the ratio crown to cation should approach 1:1 even for di-fluorenylbarium. In systems favoring 2:1 crown–cation complexes the increased distance between crown units should affect the complex formation constant, and at a low crown to styrene ratio intermolecular complex formation may occur.

The Crystal Structure of the Antitumor Agent 5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide Monohydrate Hydrochloride (NSC-45388)[1]

Steven L. Edwards, James S. Sherfinski, and Richard E. Marsh*

Contribution from the Arthur Amos Noyes Laboratory of Chemical Physics, California Institute of Technology, Pasadena, California 91109. Received September 20, 1973

Abstract: The structure of the antitumor agent 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (NSC-45388) has been investigated by single-crystal X-ray diffraction techniques. The drug crystallizes as the hydrochloride monohydrate in the monoclinic space group $P2_1/n$ with cell dimensions $a = 7.893$ (3) Å, $b = 13.961$ (2) Å, $c = 10.224$ (3) Å, $\beta = 93.20$ (4)°, $Z = 4$. Full-matrix least-squares refinement converged at a final R index of 0.058 based on 2291 counter-collected data. The molecule is nearly planar, in part held in that conformation by an internal N–H···N hydrogen bond. This intramolecular hydrogen bond may be important regarding the biological activity of this and related drugs.

Aryltriazene compounds are interesting cancer-related drugs now under investigation. The exact mechanism of the actions of these drugs is not known, but it is hypothesized that more than one mechanism may be involved. Several reports suggest that the compound 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (NSC-45388, DTIC, Figure 1a) is active as an alkylating agent.[2] The related drug 5-(3,3-bis(2-chloroethyl)-1-triazeno)imidazole-4-carboxamide (NSC-82196, DCTIC, Figure 1b) displays a different specificity to various cancers, and it has been proposed that DCTIC operates in a fashion other than that of DTIC.[3] Shealy and his coworkers[4,5] have suggested that DTIC and DCTIC both decompose to diazeno derivatives, allowing, for instance, DCTIC to liberate $NH(C_2H_4Cl)_2$.[6] This amine, nornitrogen mustard, is a known alkylating agent in itself.

Results of activity–structure studies on drugs related to aryltriazenes indicate that the terminal substituents on the triazeno group are important in determining potency.[3] At least one of these substituents must be a

methyl group or the compound is inactive. The exception to this rule is the case of DCTIC which, as evidenced above, acts by a different mechanism. Substituting a benzene ring for the imidazole ring has little effect on activity.[7]

Although the crystallization of DCTIC has not yet been successful, the crystal structures of its transformation product[8] (Figure 1c) and of a pyrazole derivative[9] (Figure 1d) have been reported. This paper presents the results of a crystallographic investigation of DTIC, 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide, as the hydrochloride monohydrate.

Experimental Section

A sample of DTIC was supplied by Dr. Corwin Hansch of Pomona College. A small amount was dissolved in a toluene-glacial acetic acid solution and placed in a desiccator charged with $CaCl_2$. Clear, well-shaped, prismatic crystals formed within a few days. Precession photographs indicated a monoclinic unit cell and space group $P2_1/n$ (systematic absences: $0k0$, k odd; $h0l$, $h + l$ odd). Accurate cell dimensions were obtained by a least-squares fit to the observed $\sin^2 \theta/\lambda^2$ values for 16 reflections as measured on a diffractometer; the density was measured by flotation in a bromobenzenechlorobenzene solution. Crystal data are given in Table I.

The measured density is in fair agreement with the value 1.43 g/cm^{-3} calculated for four molecules of DTIC and four molecules of acetic acid per unit cell, and we presumed the crystals to have that composition. It was only during the course of the structure solution that it became apparent that the compound was actually the hydrochloride monohydrate salt, rather than the acetate. We

(1) Contribution No. 4734 from the Arthur Amos Noyes Laboratory of Chemical Physics. This investigation was supported in part by Public Health Service Grant No. GM 16966 from the National Institutes of Medical Sciences, National Institutes of Health. One of us (J. S. S.) would like to acknowledge the support of an NIH Traineeship.
(2) J. Luce, W. Thurman, B. Isaacs, and R. Talley, *Cancer Chemother. Rep.*, **54**, 122 (1970).
(3) C. Hansch, N. Smith, R. Engle, and H. Wood, *Cancer Chemother. Rep.*, **56**, 443 (1972).
(4) Y. F. Shealy, J. A. Montgomery, and W. R. Laster, Jr., *Biochem. Pharmacol.*, **11**, 674 (1962).
(5) Y. F. Shealy, R. P. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.*, **26**, 2396 (1961).
(6) C. L. Vogel, C. Denham, T. P. Waalkes, and T. De Vita, *Cancer Res.*, **30**, 1651 (1970).

(7) Y. T. Lin, T. L. Loo, S. Vadlomudi, and A. Goldin, *J. Med. Chem.*, **15**, 201 (1972).
(8) D. Abraham, J. Rutherford, and R. Rosenstein, *J. Med. Chem.*, **12**, 189 (1969).
(9) J. E. Whinnery and W. H. Watson, *Acta Crystallogr.*, *Sect. B*, **28**, 3635 (1972).