diluted with 150 mL of water, and extracted 5 times with 15-mL portions of methylene chloride. The combined extracts were dried over a mixture of Na_2SO_4–$NaHCO_3$, and most of the solvent was removed by distillation to yield 0.1 g (30%) of residue. The residue on analysis by gas chromatography (6 ft × $^1/_8$ in., 15% DEGS on 80/100 Chrom WHP column, 75 °C, 38 mL/min He flow rate) in addition to the solvent peak gave rise to one minor peak, A (t_R 1.9 min), and two major peaks, B (t_R 2.9 min) and C (t_R 3.5 min) with 1.0:1.3 relative peak areas. On the basis of retention times, as compared to known samples, peak B was identified as ethyl 2-methyl-3-(trifluoromethyl)butyl ether and peak C was identified as 2-methyl-3-(trifluoromethyl)-2-butanol.

Solvents. Acetic acid solvent was prepared from 994.9 mL of glacial acetic acid (J. T. Baker Chemical Company) and 5.1 mL of acetic anhydride. Formic acid solvent was prepared by storing practical grade formic acid (Matheson, Coleman, & Bell, 97–100%) over boric anhydride for several days, decanting, and distilling from fresh anhydride. Ethanol solvent was prepared according to the method of Fieser.[52] The water solvent was purified by passage through a mixed bed deionizer to produce water of 17 $\mu\Omega$ or better quality.

Rate Measurements. The rates of solvolysis were followed titrimetrically. In a typical run, the requisite amount of sulfonate ester was accurately weighed into a 25-mL volumetric flask and then sufficient solvent was added rapidly to give a 25-mL reaction solution volume.[53] Reaction time commenced with the addition of the solvent. At appropriate times, 2-mL aliquots were analyzed for liberated sulfonic acid. The titrating solutions were as follows: for acetic–formic acid solvents, 0.02 N sodium acetate in acetic acid; and for the aqueous ethanol solvents, 0.02 N sodium methoxide in methanol. The indicators used were as follows: for acetic–formic acid solvents, bromophenol blue in acetic acid (2–3 drops); for aqueous ethanol solvents, bromothymol blue in water (2 drops).

Treatment of Kinetic Data. First-order rate constants were calculated by using the integrated first-order rate equation[54,55]

$$k_t = 1/t \ln (\mathrm{mL}_\infty/\mathrm{mL}_\infty - \mathrm{mL}_t)$$

Multiple determinations (6–12) were made for each kinetic run. The slope values recorded in Table IV were obtained by regression analysis[56] of log k_t(Y) versus: log k_t(neophyl-OTs) values,[1f] Y_{OTf} values,[24] Winstein–Grunwald Y values,[18] and Y_{OTs} values[57] as indicated in the table.

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[53] For reactions whose half-lives were longer than a few weeks, rate measurements were accomplished by the ampule technique.[1f]

[54] (a) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; Wiley: New York, 1961. (b) Carpenter, R. G. *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984; Chapter 4.

[55] The parameter mL_∞ = measured titer at 10 half-lives or theoretical titer at 100% conversion calculated from known quantity of sulfonate ester present in the reaction mixture; mL_t = measured titer at time t.

[56] (a) Edwards, A. L. *An Introduction to Linear regression and Correlation*; W. H. Freeman and Co.: San Francisco, 1976; pp 21–32. (b) Dixon, W. J.; Massey, F. J. *Introduction to Statistical Analysis*; McGraw-Hill: New York, 1957; pp 191–192.

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Ion Pairing and Reactivity of the Alkali-Metal and Alkaline-Earth-Metal Derivatives of Ethyl (5-Bromopentyl)acetoacetate

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The effect of added alkali-metal and alkaline-earth-metal salts on the rate of intramolecular alkylation of the title compound has been investigated in 99% aqueous Me_2SO. It was found that the rate is practically insensitive to Et_4N^+ and K^+ ions and it is slightly decreased by Na^+ ion, but it is strongly depressed by Li^+, Ba^{2+}, Sr^{2+}, Ca^{2+}, and Mg^{2+} ions, the observed effects ranging over nearly 5 powers of ten. Analysis of rate data was carried out by means of a self-consistent approach, as based on the classical Acree hypothesis of independent contributions of free ions and ion pairs to the overall rate. In most cases it was possible to measure the ion pairing association constants (K_{ip}) together with the specific rates for reactions of the ion pairs (k_{ip}), even when the latter are much lower than the specific rate for reaction of the free ion (k_{i}). The results show that ion pairing decreases in the order Li > Na > K and Mg > Ca > Sr > Ba, which clearly suggests that association is dominated by coulombic interactions. The strong inhibition caused by ion pairing is due to a greater cation interaction with the anionic reactant than with the transition state, where a significant fraction of the available negative charge is concentrated in the C–C bond-forming region.

It has been recognized for many years that cation association may greatly affect the reactivities of anionic nucleophiles such as alkoxides, aryloxides, and enolates in nucleophilic substitution and addition reactions.[1-3] It is worth noting, however, that knowledge in the field is mainly based on evidence which is qualitative in nature, or semiquantitative at best. Relatively few quantitative studies have been reported in recent years.[4-9] It has been

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[1] le Noble, W. J. *Highlights of Organic Chemistry*; Marcel Dekker: New York, 1974; Chapter 22.

[2] Reutov, O. A.; Kurts, A. L. *Russ. Chem. Rev. (Engl. Transl.)* 1977, *46*, 1040.

[3] Jackman, L. M.; Lange, B. C. *Tetrahedron* 1977, *33*, 2737.

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[7] Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* 1983, *105*, 555.

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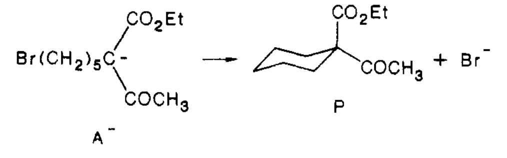
pointed out[6,8] that a major difficulty in these studies arises from a meaningful dissection of contributions to the overall rate into separate contributions of rapidly equilibrating free ions, ion pairs, and higher aggregates.

Our previous work on the effect of alkali-metal ions on the reactivity of aryloxide ions[7] and of the anion derived from a malonic ester derivative[8] in alkylation reactions of the S_N2 type has shown that under suitable conditions a self-consistent analysis of rate data leads to a satisfactory solution of the problem in terms of cation association with both initial and transition state. This is operationally equivalent to a dissection of contributions of free ions and ion pairs to the overall rate.

In view of the general importance of the β-keto enolates derived from acetoacetic esters, and as a continuation of our studies in the field, we have undertaken a detailed investigation of the effect of added alkali-metal and alkaline-earth-metal ions on the rate of cyclization of the anion derived from ethyl (5-bromopentyl)acetoacetate in 99% aqueous Me_2SO (v/v) at 25 °C (eq 1). The results of such an investigation, together with a self-consistent analysis of rate data, are reported herein. The ultimate goal of these investigations is the collection of a body of experimental information, namely, association constants of metal cations with anionic nucleophiles and transition states, to provide a sound basis for interpretation of association phenomena in terms of cation size and charge and anion structure.



(1)

Results and Discussion

Cyclization of A^- as the reaction of choice for the present investigation offers several advantages. First, only monoalkylation is possible, as only one acidic proton is present in the parent compound AH. Second, any complication due to competing C- and O-alkylation is absent, since O-alkylation would lead to a highly disfavored eight-membered ring. Product analysis showed that under the conditions of the kinetic runs 1-acetyl-1-(ethoxycarbonyl)cyclohexane was the only detectable product (Experimental Section). Finally, the reaction rate in the absence of added salts lies conveniently in the stopped-flow range. An intrinsically slower reaction would lead to rates unconveniently low to measure because of the strong rate-retarding effects exerted by some of the added salts.

The kinetics were followed by monitoring the disappearance of the enolate ion absorption in the neighborhood of 300 nm. The reactant concentration was typically in the order of 1.5×10^{-4} mol L^{-1}. The anion was generated in situ by addition of a calculated amount of Me_4NOH to a solution of the parent reactant AH and salt.[10] The Et_4N^+ ion and the metal cations were added as bromides, with the sole exception of Mg^{2+}, which was added as perchlorate, because of the difficulty of obtaining anhydrous $MgBr_2$. Good first-order behavior was observed in all cases up to high conversions. The observed rate constants k_{obs} are listed in the Experimental Section and are plotted against the concentration of added salt in Figure 1.

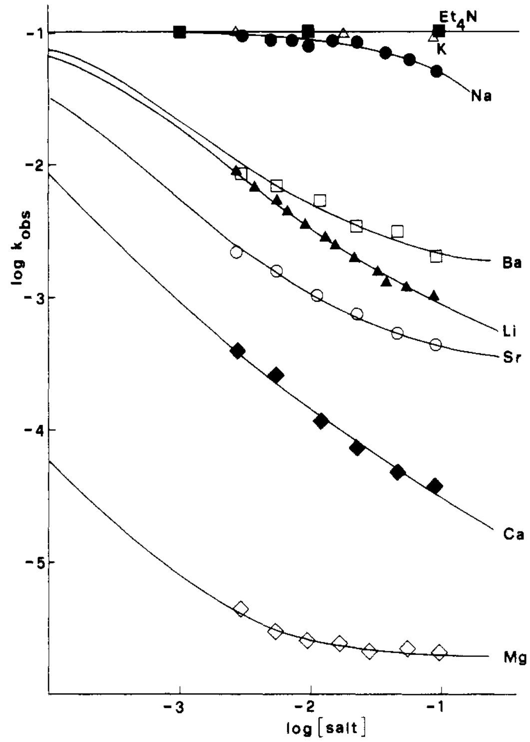
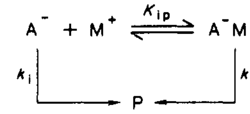


Figure 1. Effect of tetraethylammonium and metal salts on the rate of intramolecular alkylation of β-keto enolate A^- in 99% Me_2SO. The horizontal line represents the specific rate k_i for reaction of the free ion. The points are experimental (k_{obs} in s^{-1}) and the lines are calculated by using eq 2.

Scheme I



Analysis of rate data was carried out on the basis of a distribution scheme involving independent contributions from the free ion A^- and from the ion pair A^-M^+ (Scheme I). If one assumes that the activity coefficients of the transition states from A^- and from A^-M^+ are identical with those of A^- and A^-M^+, respectively, which is equivalent to the assumption of a negligible primary salt effect on what is essentially the intramolecular version of a reaction involving an ion and a neutral molecule, eq 2 is easily obtained.[11] The latter relates the measured quantity k_{obs}

$$k_{obs} = k_i \frac{1 + (k_{ip}/k_i)K_{ip}\gamma_\pm^2[M^+]}{1 + K_{ip}\gamma_\pm^2[M^+]} \qquad (2)$$

to $[M^+]$ through a functional relation which reduces to a two-parameter equation when k_i is known.

We first note that E_4N^+ and K^+ exert but a negligible influence on the reaction rate. Although eq 2 predicts no influence on k_{obs} not only when K_{ip} is small, but also when $k_{ip} = k_i$ for any value of K_{ip}, for the sake of internal consistency in the present work and in the line with previous results from our[7,8] and other[5,6] laboratories, we believe it

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[9] Crescenzi, M.; Galli, C.; Mandolini, L. *J. Chem. Soc., Chem. Commun.* **1986**, 551.

[10] With the exception of runs carried out in the presence of Et_4NBr, KBr, and NaBr, we observed a relatively slow production of the enolate absorption upon addition of the base, showing that those ions which strongly inhibit the reaction of A^- also inhibit the reaction of OH^- with AH. This phenomenon did not interfere with the rate measurements, since in all cases the rate of production of A^- was much faster than its subsequent decay.

[11] Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970; pp 211-213.

Table I. Ion Pairing Association Constants and Reactivity of Ion Pairs

metal ion	log K_{ip}	log $K_{\neq}$	k_{ip} (s^{-1})	k_{ip}/k_i[a]
K^+	<1			
Na^+	1.40			≪1
Li^+	3.72	1.32	4.1×10^{-4}	4.0×10^{-3}
Ba^{2+}	3.66	1.87	1.6×10^{-3}	1.6×10^{-2}
Sr^{2+}	4.32	1.81	3.1×10^{-4}	3.0×10^{-3}
Ca^{2+}	5.08	1.11	1.1×10^{-5}	1.0×10^{-4}
Mg^{2+}	⩾7	⩾2	1.8×10^{-6}	1.7×10^{-5}

[a] $k_i = 0.102\ s^{-1}$.

more reasonable to conclude that association of A^- with either Et_4N^+ or K^+ is neglibibile, i.e., $K_{ip} < 10$. Thus, the k_{obs} value of 0.102 s^{-1} obtained when the Me_4N^+ ion accompanying the added base is the sole counterion was taken as a reliable measure of the specific rate k_i for the reaction of the free ion A^-. In all the other cases significant rate-retarding effects are apparent, which are markedly dependent upon cation nature and concentration. Since the alkali-metal bromides behave as strong electrolytes in Me_2SO,[7] and since in all cases the concentration of added salt was much greater than the substrate concentration, the total concentration of added salt was taken as a reasonable approximation for $[M^+]$. A nonlinear least-squares procedure (see Experimental Section) was used to fit eq 2 to the k_{obs} values obtained in the presence of Na^+ and Li^+. The good agreement between the experimental points and the full lines calculated by means of the least-squares parameters (Figure 1) clearly shows that distribution Scheme I adequately describes the metal ion effects on the rate of reaction (1). In order to extend the quantitative treatment to the rate-retarding effects exerted by the divalent metal salts, we have tentatively assumed that the latter behave as strong 1:1 electrolytes of the $(MX)^+X^-$ type in Me_2SO solution. Accordingly, the quantity $[M^+]$ in eq 2 was set equal to the total salt concentration and the least-squares fit of the data to eq 2 was carried out on this basis. The close adherence of the experimental data to eq 2 (Figure 1) provides a good indication of the essential correctness of the above assumption.

The results of the analysis of rate data are collected in Table I. The quantities listed in the second column of Table I were calculated from eq 3, which is derived from

$$K_{\neq} = (k_{ip}/k_i)K_{ip} \qquad (3)$$

the transition-state theory.[11] $K_{\neq}$ has the meaning of the equilibrium constant for the formal reaction of the transition state that does not contain M^+ into the one that contains M^+, i.e., the ion pairing association constant of the transition state. This quantity has proved useful in discussions of structure effects on reactivity of ion pairs relative to free ions in terms of relative stabilities of ion pairs with transition states and reactants.[7,8]

Table I shows that the extent of association of the β-keto enolate ion A^- with the alkali-metal and alkaline-earth-metal ions depends in a dramatic way upon cation nature, the association constants spanning a range of more than 6 orders of magnitude. Among the alkali-metal ions, association constants decrease markedly in the order Li > Na > K, which is the trend observed in Me_2SO for many β-keto enolate ions which can adopt a U-type conformation,[4,8,12] as well as for alkoxide[13] and aryloxide[7] ions. This finding clearly indicates that the stability order among ion pairs is dominated by the stronger coulombic interaction with the smaller metal ions, and not by solvation effects, which would lead to an opposite trend.[7,8,12] This conclusion is fully consistent with the behavior exhibited by the alkaline-earth-metal ions, for which the extent of cation association grades regularly in the order Mg > Ca > Sr > Ba.

When compared with the log K_{ip} values, the corresponding log $K_{\neq}$ values show that cation interactions with the transition state are not only much weaker but also much less dependent on cation nature, the observed $K_{\neq}$ values ranging over about 1 order of magnitude. This is in line with expectations,[8] since a significant fraction of the negative charge of A^- is concentrated in the C–C bond-forming region in the transition state and, consequently, is less available for cation interaction. On this basis the cation dependence of the ion pair reactivity is easily understood, remembering that $k_{ip}/k_i = K_{\neq}/K_{ip}$. Since the stabilities of the ion pair transition states are only slightly cation-dependent, the principal variable in the measured k_{ip}/k_i values is K_{ip}, and the differences in this equilibrium constant are the principal cause for the differences in ion pair reactivity. Thus, it is not surprising to find that there is an approximately inverted relationship between stability and reactivity of the A^-M^+ pairs.

Experimental Section

Ethyl (5-bromopentyl)acetoacetate was prepared according to a literature procedure,[14] ^1H NMR as expected. The alkali-metal and alkaline-earth-metal bromides $Mg(ClO_4)_2$ and Et_4NBr (AR grade materials) were dried under vacuum.

Rate Measurements. These were carried out as previously reported[8] by using either conventional or stopped-flow spectrophotometry. The mixed solvent (99% aqueous Me_2SO, v/v) and the Me_4NOH stock solution were prepared and handled as previously described.[8] Rate constants k_{obs} (s^{-1}) are listed below at the various added salt concentrations, which are given in parentheses in mol L^{-1}. $k_i = 0.102 \pm 0.004$ (no added salt).

Et_4NBr: 0.104 (1.00×10^{-3}); 0.101 (1.00×10^{-2}); 0.100 (1.00×10^{-1}).

KBr: 9.35×10^{-2} (2.81×10^{-3}); 9.27×10^{-2} (1.87×10^{-2}); 9.16×10^{-2} (9.36×10^{-2}).

NaBr: 9.35×10^{-2} (3.01×10^{-3}); 8.51×10^{-2} (5.02×10^{-3}); 8.71×10^{-2} (7.54×10^{-3}); 7.82×10^{-2} (9.85×10^{-3}); 9.11×10^{-2} (1.52×10^{-2}); 8.44×10^{-2} (2.29×10^{-2}); 7.02×10^{-2} (3.81×10^{-2}); 6.10×10^{-2} (5.72×10^{-2}); 5.09×10^{-2} (9.48×10^{-2}).

LiBr: 8.92×10^{-3} (2.84×10^{-3}); 6.73×10^{-3} (3.79×10^{-3}); 5.40×10^{-3} (5.69×10^{-3}); 4.34×10^{-3} (6.64×10^{-3}); 3.41×10^{-3} (9.48×10^{-3}); 2.82×10^{-3} (1.33×10^{-2}); 2.49×10^{-3} (1.52×10^{-2}); 1.99×10^{-3} (2.27×10^{-2}); 1.56×10^{-3} (3.41×10^{-2}); 1.26×10^{-3} (3.79×10^{-2}); 1.21×10^{-3} (5.69×10^{-2}); 9.93×10^{-4} (9.48×10^{-2}).

$BaBr_2 \cdot 2H_2O$: 8.39×10^{-3} (2.83×10^{-3}); 6.65×10^{-3} (5.66×10^{-3}); 5.40×10^{-3} (1.23×10^{-2}); 3.36×10^{-3} (2.36×10^{-2}); 3.11×10^{-3} (4.72×10^{-2}); 1.97×10^{-3} (9.43×10^{-2}).

$SrBr_2 \cdot H_2O$: 2.20×10^{-3} (2.82×10^{-3}); 1.55×10^{-3} (5.65×10^{-3}); 1.04×10^{-3} (1.18×10^{-2}); 7.36×10^{-4} (2.35×10^{-2}); 5.19×10^{-4} (4.71×10^{-2}); 4.21×10^{-4} (9.41×10^{-2}).

$CaBr_2 \cdot 2H_2O$: 3.84×10^{-4} (2.80×10^{-3}); 2.59×10^{-4} (5.61×10^{-3}); 1.11×10^{-4} (1.22×10^{-2}); 7.17×10^{-5} (2.34×10^{-2}); 4.44×10^{-5} (4.67×10^{-2}); 3.64×10^{-5} (9.35×10^{-2}).

$Mg(ClO_4)_2$: 4.25×10^{-6} (2.99×10^{-3}); 2.71×10^{-6} (5.50×10^{-3}); 2.43×10^{-6} (9.98×10^{-2}); 2.36×10^{-6} (1.70×10^{-2}); 2.05×10^{-6} (2.99×10^{-2}); 2.10×10^{-6} (5.50×10^{-2}); 1.93×10^{-6} (9.98×10^{-2}).

The k_{obs} values were fitted by means of a nonlinear least-squares procedure[15] to an equation of the form (4), where $y = (k_{obs}/k_i)$

$$y = \frac{1 + Ax}{1 + Bx} \qquad (4)$$

and $x = \gamma_{\pm}^2[M^+]$. The mean activity coefficient $\gamma_{\pm}$ was calculated as before[7] from eq 5. The least-squares calculations, carried out

$$\log \gamma_{\pm} = -1.12\mu^{1/2} + 1.65\mu \qquad (5)$$

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on a Apple II microcomputer, afforded the following numerical values for the A and B parameters, which are reported in the given order for the various cations: Li^+, 21, 5.2×10^3; Ba^{2+}, 75, 4.6×10^3; Sr^{2+}, 65, 2.1×10^4; Ca^{2+}, 13, 1.2×10^5; Mg^{2+}, 354, 2.1×10^7. For Na^+, $B = 25$, but A is so small that it is devoid of physical significance. The A and B values were translated by means of eq 2 and 3 into the rate and equilibrium constants listed in Table I. It should be noted that the figures reported for Mg^{2+} are not meaningful as such, as in this case the products Ax and Bx are greater than one in the whole concentration range. As a consequence, the quantity y is very close to the limiting value A/B approached at high cation concentrations. The ratio $A/B = k_{ip}/k_i$ is highly significant, however. It is determined in this case with an inherent precision which is higher than those obtained with the other salts.

Product Analyses. These were carried out on scaled-up kinetic runs. GLC analyses[8] were carried out at 125 °C, using hexadecane as the internal standard. The yield of 1-acetyl-1-(ethoxycarbonyl)cyclohexane was 75% in the absence of added salt, 88% in the presence of 0.1 M LiBr, and 75% in the presence of 1.7×10^{-2} M $Mg(ClO_4)_2$.

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Registry No. A^-, 113997-12-9.

Amino Acid Containing Macrocycles. Synthesis, Complexation of Water, and Transport and Binding of Metal Cations

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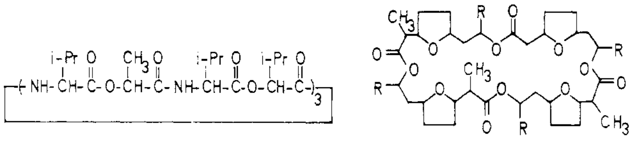
A series of macrocycles incorporating two α-phenylglycine and a variable number of ethyleneoxy units have been prepared as new ionophore models. Transport studies (U-cell, chloroform liquid membrane) showed that only 24-membered macrocycles **8** mimic naturally occurring cyclic ionophores (valinomycin, nonactin) in their ability to transport K^+ and Na^+ ions across the lipophilic membrane. *meso*-**8** was found to be a more efficient ion carrier than (±)-**8** for M^+ picrates ($K^+ > Na^+ > Rb^+ > Cs^+$). However, both ligands exhibited negligible transport of M^{2+} (Ba^{2+}, Sr^{2+}, Mg^{2+}, Ca^{2+}) picrates. *meso*-**8** and (±)-**8** exhibited poor extraction equilibrium constants ($K_{ex} = 164$ and 83 M^{-2}, respectively) for K^+ picrate in a chloroform–water system. ^1H and ^{13}C NMR studies of complexation with (±)- and *meso*-**8** and K^+, Na^+, Ba^{2+}, and Mg^{2+} salts in $CDCl_3/CD_3CN$ solvent mixture showed that ligands **8** bind metal cations by the mutual assistance of amide carbonyl or ester carbonyl and ether oxygen donors. In this work the first crystalline complex with a macrocycle of this type and a metal cation was obtained, from *meso*-**8** and KSCN. 24-Membered ligands (±)-**8** and *meso*-**8** form considerably more stable water complexes in chloroform than the equally large crown ethers.

Naturally occurring macrocyclic ionophores such as valinomycin and nactins exhibit highly selective transport of K^+ ions across biological and artificial membranes.[1] This property is the cause of their antibiotic activity.[2] Both kinds of natural ionophores bind metal cations in the central cavity of the macroring by ion–dipole interactions with ester carbonyls (valinomycin[3,4]) or with ester carbonyls and ether oxygens (nactins[5]). High selectivities exhibited in the transport of metal cations are a consequence of the specific, rigid conformations of valinomycin and nactins in their cationic complexes.[3,6] These unique properties of valinomycin and nactins present a challenge from the synthetic as well as the biological point of view.

Chart I



Valinomycin Nactins

Several attempts have been made to mimic valinomycin and nonactin activities by using synthetic polyether macrocycles. In one approach, 18- and 19-membered dilactone analogues of 18-crown-6 were studied as valinomycin models.[7] However, the ring size of the model dilactones studied was too small to permit the ester carbonyls to turn inward and take part in the complexation of cations.[8] On the other hand, 32-membered tetralactone cyclopolyethers were studied as nactin models.[9] These tetralactones achieved only slow transport and poor K^+/Na^+ selectivity in comparison to nonactin due to the greater flexibility of model macrocycles. Nitrogen-pivot

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