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Lack of a "Cesium Effect" on Macrolactonization

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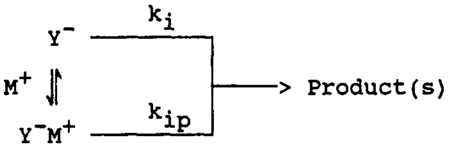
The lactonization of ω-bromoalkanoate ions, run in DMF under preparative conditions and in the presence of various counterions, is exploited to show that those synthetic effects whose manifestation has led to the coinage of the term "cesium effect" are simply due to the operation of well-established, rate-decreasing ion-pairing phenomena upon the reactivity of anionic nucleophiles. No peculiarity emerges with cesium when compared with the other alkali-metal ions.

Following earlier reports on the efficient alkylation of cesium carboxylates with alkyl halides in dimethylformamide (DMF),[1] a host of papers have appeared wherein the synthetic usefulness of cesium salts of weak organic acids in S_N2-type macrocyclization reactions of α,ω-bifunctional reactants has been praised.[2,3] Typical comments about this beneficial, almost thaumaturgical property of cesium ion, the so-called "cesium effect", include the following: "cesium ion, relative to other alkali metal cations, appears to direct the reaction in an intramolecular fashion";[3] "strained or overcrowded large-ring sulfides can be obtained if the usual cyclization reaction is carried out in the presence of cesium ion";[4] "benefit was taken from the ability of the cesium ion to gather fragments for S_N2 actions".[5,6]

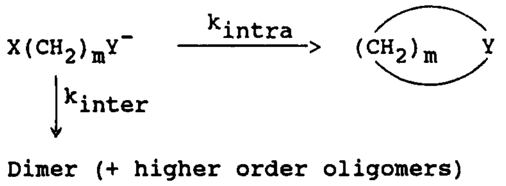
In terms of the well-known Acree's concept[7] of free (Y^-) and cation-paired (Y^-M^+) nucleophiles acting as independent kinetic entities (Scheme I), the operation of a "cesium effect" that alters the competition between macrocyclization and polymerization (Scheme II) would imply (i) that the ion pair gives an appreciable contribution to the overall rate and (ii) that the k_{intra}/k_{inter} ratio for the ion-pair path is greater than that for the free-ion path, namely, $(k_{intra}/k_{inter})_{ip} > (k_{intra}/k_{inter})_i$, or at least greater than the corresponding quantities for reactions of other alkali-metal ions.[8]

In fact, as a first attempt at an interpretation of the phenomenon, Kruizinga and Kellogg[10] speculated that a facile intramolecular reaction, but not the corresponding intermolecular reaction, would take place on the surface of the large, polarizable metal ion in a tight carboxylate–cesium ion pair, but subsequent attempts at detecting the ion pair in DMF solution by means of ^{133}Cs NMR failed.[3]

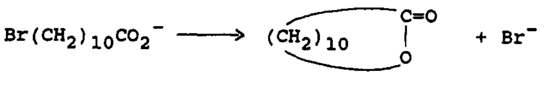
Scheme I



Scheme II



In a recent investigation of ion-pairing effects on rates of lactonization of ω-bromoalkanoates in dipolar aprotic solvents (99% Me_2SO and DMF),[11] we found that pairing of alkanoate ions with alkali-metal ions is in all cases rate-depressing, to extents closely reflecting the strength of interaction of carboxylate with the metal ion. But even more importantly, contributions to the overall rate from associated species turned out to be negligible, or very nearly so, in comparison with contributions from free ions, even under conditions where most of the carboxylate ions were in the associated form. These findings strongly reinforced our earlier[12] reservations about the mere existence of a "cesium effect", at least under homogeneous conditions, and prompted us to undergo the present investigation, with the aim of establishing a closer link between the kinetic investigation, as carried out under homogeneous conditions, and the preparative experiments, which are generally carried out in the presence of solid alkali carbonates.[10] The experiments performed are divided into three parts. The first one consists of rate measurements showing that metal ion effects on intramolecular cyclization are closely paralleled by metal ion effects on an intermolecular model reaction. In the second part, metal ion effects on yields of lactone from 11-bromoundecanoate ion were investigated under homogeneous conditions in order to allow a close comparison with results from the kinetic investigation. Since metal ion effects on reaction rates of anionic nucleophiles are strongly concentration-dependent, and since macrocycle syntheses under batchwise conditions are per force carried out at fairly low substrate concentrations, as obviously demanded by the high-dilution requirements,[13,14] we have resorted to the usual technique[11] of adding varying amounts of alkali-metal salts as external electrolytes in order to vary, over a wide range, the proportions of free carboxylate to metal-associated



(1)

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[1] (a) Gisin, B. F. *Helv. Chim. Acta* **1973**, *56*, 1476. (b) Wang, S.-S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, I. D.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286.

[2] Klieser, B.; Rossa, L.; Vögtle, F. *Kontakte (Darmstadt)* **1984**, No. 1, 3.

[3] Dijkstra, G.; Kruizinga, W. K.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230. See also references therein.

[4] Vögtle, F.; Klieser, B. *Synthesis* **1982**, 294.

[5] Wytko, J. A.; Weiss, J. *J. Org. Chem.* **1990**, *55*, 5200.

[6] The argument runs that cesium ion is believed to be capable of joining together the two ends of the macrocycle precursor, thus facilitating ring closure at the expense of polymerization.

[7] Acree, S. F. *Am. Chem. J.* **1912**, *48*, 352.

[8] Similar considerations apply if Scheme I is to be expanded to include ion triplets and higher aggregates. See ref 9.

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

[10] Kruizinga, W. K.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183.

[11] Crescenzi, M.; Galli, C.; Mandolini, L. *J. Phys. Org. Chem.* **1990**, *3*, 428.

[12] Galli, C.; Mandolini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 251.

[13] Rossa, L.; Vögtle, F. *Top. Curr. Chem.* **1983**, *113*, 1.

[14] Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1.

Table I. Effect of Added Salts on the Rates of Intramolecular and Intermolecular Alkylation of Carboxylate Anion in DMF at 45 °C

added salt, 0.05 M	intra[a] k_{intra}, s^{-1}	intra[a] k_{rel}	inter[b] k_{inter}, $M^{-1}\ s^{-1}$	inter[b] k_{rel}	EM,[c] M
Et_4NBr	4.3×10^{-3}	1.0	1.7×10^{-1}	1.0	2.5×10^{-2}
$CsClO_4$	1.3×10^{-3}	0.30	4.8×10^{-2}	0.28	2.7×10^{-2}
$NaClO_4$	2.4×10^{-4}	0.056	1.0×10^{-2}	0.058	2.4×10^{-2}

[a] Lactonization of 1.00×10^{-3} M $Br(CH_2)_{14}CO_2^-Bu_4N^+$. [b] Alkylation of 1.00×10^{-3} M $CH_3(CH_2)_4CO_2^-Bu_4N^+$ with 4.00×10^{-3} M BuBr. [c] Calculated as $k_{\mathrm{intra}}/k_{\mathrm{inter}}$.

carboxylate (Scheme I). In the third part, yields of lactone, in what is essentially Kellogg's macrolactonization procedure,[10] namely, treatment of the bromo acid precursor in DMF with excess alkali-metal carbonate, were carefully measured for the various alkali-metal carbonates. The results of this investigation are reported herein.

Results and Discussion

Ion-Pairing Effects on Intramolecular vs Intermolecular Substitution. As the crucial point in the whole question of the cesium effect is whether or not polymerization is disfavored relative to cyclization, we have preliminarily carried out a comparison of counterion effects on the rates of lactonization of 15-bromopentadecanoate anion (16-membered-ring formation) and of the intermolecular related reaction, that is, the alkylation of hexanoate anion with butyl bromide under strictly comparable conditions. Both reactions were carried out in DMF at 45 °C on very dilute solutions (0.001 M) of the tetrabutylammonium salts of the alkanoate ions, in the presence of a large excess (0.05 M) of an added electrolyte (Et_4NBr, $NaClO_4$, $CsClO_4$). Et_4NBr was chosen as the reference, since ion pairing of Et_4N^+ with carboxylate is known to be negligible, or very nearly so.[11] Consistent with previous findings,[11] the data listed in Table I show that the effect of the alkali-metal ions is rate-depressing and that the intramolecular reaction is affected much in the same way as the intermolecular reaction. The is clearly equivalent to saying that EM[15] is virtually insensitive to the nature of the counterion, which is exactly what is expected for reactions proceeding via the free ion. Therefore, however complex the structure of the ion-paired species, i.e., whether ion triplets or higher aggregates are present under these conditions, and however complex the structure of the solution at this relatively high ionic strength, this comes out to be irrelevant to the behavior of the reactive free-ion species. Incidentally, we note that the EM values listed in Table I compare very well with the value of 2.9×10^{-2} M determined in 99% aqueous Me_2SO at 50 °C.[16]

Table II. Effect of Added Salts on the Yield of 11-Undecanolide from $Br(CH_2)_{10}CO_2^-Bu_4N^+$ in DMF at 45 °C[a]

added salt (MX)	reaction time, h	lactone yield, % [MX] = 8×10^3	lactone yield, % [MX] = 0.05	lactone yield, % [MX] = 0.2
Bu_4NBr	1.5	82 ± 2	62 ± 1	63 ± 2
$CsClO_4$	1.5	81 ± 1	59 ± 2	52 ± 2
KBr	1.5	80 ± 2	57 ± 2	*b*
$NaClO_4$	1.5	76 ± 2		11 ± 2
NaBr	1.5	77 ± 2	26 ± 2	11 ± 2
$LiClO_4$	1.5	19 ± 2		
LiBr	1.5	22 ± 2		<1
LiBr	15			26 ± 2
LiBr	150			52 ± 2

[a] $[Br(CH_2)_{10}CO_2^-Bu_4N^+]_0 = 4.0 \times 10^{-3}$. In the absence of added salts, the yield of 11-undecanolide is 83 ± 1%. [b] Experiment prevented by the low solubility of KBr.

Table III. Lactonization of 11-Bromoundecanoic Acid in the Presence of Alkali-Metal Carbonates[a]

alkali-metal carbonate	yield,[b] %
Li_2CO_3	22 ± 1
Na_2CO_3	78 ± 2
K_2CO_3	80 ± 2
Cs_2CO_3	82 ± 1

[a] Reaction carried out in DMF at 80 °C. Reaction time, 120 min. $[Br(CH_2)_{10}CO_2H]_0 = 2.2 \times 10^{-3}$. [b] GLC yield of 11-undecanolide.

Macrolactonization under Homogeneous Conditions. In order to assess the counterion effect on yields of lactone formation in the absence of any possible interference from heterogeneity, cyclization of the tetrabutylammonium salt of 11-bromoundecanoic acid, generated in situ by mixing equimolar amounts of acid and tetrabutylammonium hydroxide, was carried out in DMF at 45 °C in the presence of three different concentrations of added salts, namely, 0.008, 0.05, and 0.2 M. In all cases, the initial concentration of 11-bromoundecanoate was 4.0×10^{-3} M. In most experiments the reaction was stopped after 90 min, and the yield of 11-undecanolide (1) was determined by GLC (internal standard) after the workup. The results are summarized in Table II. 11-Bromoundecanoic acid was the substrate of choice because, unlike 15-bromopentadecanoic acid, at the very low initial concentration of 4.0×10^{-3} M its cyclization is still accompanied by polymerization to a significant extent.[16] The maximum yield of lactone to be obtained for a complete conversion of the reactant can be calculated to a reasonable approximation by means of eq 2,[14,17] which relates the (normalized) yield of monomeric macrocycle to the dimensionless parameter α defined as $[M]_0/(k_{\mathrm{intra}}/k_{\mathrm{inter}})$, where $[M]_0$ is the initial reactant concentration.[18] If one

$$\text{yield} = \frac{1}{2\alpha} \ln (1 + 2\alpha) \qquad (2)$$

makes the reasonable assumption that the $k_{\mathrm{intra}}/k_{\mathrm{inter}}$ value (EM) for cyclization of the 11-bromoundecanoate anion in DMF is the same as in 99% Me_2SO, namely, 6.0×10^{-3} M,[16] the yield of 1 calculated from eq 2 is 72%. However, the above figure is most likely underestimated, because the intermolecular model reaction chosen for the evaluation of k_{inter}, namely, the alkylation of butanoate anion with butyl bromide, eq 3,[16] does not take into account the repulsion of the negative charges taking place in the actual dimerization process, eq 4, which competes with macrocyclization. A direct determination of k_{dim} is available for

$$CH_3(CH_2)_2CO_2^- + CH_3(CH_2)_3Br \xrightarrow[-\mathrm{Br}^-]{k_{\mathrm{inter}}} CH_3(CH_2)_2CO_2(CH_2)_3CH_3 \qquad (3)$$

$$Br(CH_2)_{10}CO_2^- + Br(CH_2)_{10}CO_2^- \xrightarrow[-\mathrm{Br}^-]{k_{\mathrm{dim}}} Br(CH_2)_{10}CO_2(CH_2)_{10}CO_2^- \qquad (4)$$

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(15) The effective molarity (EM) is defined by the ratio $k_{\mathrm{intra}}/k_{\mathrm{inter}}$ (Scheme II). It has the physical meaning of the substrate concentration at which cyclization and polymerization occur with the same rate. For a thorough discussion of the relation between EM and synthesis of ring compounds, see ref 14.

(16) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591.

(17) Galli, C.; Mandolini, L. *Gazz. Chim. Ital.* **1975**, *105*, 367.

(18) For more sophisticated treatments of competing macrocyclization and polymerization, see: (a) Ercolani, G.; Mandolini, L.; Mencarelli, P. *Macromolecules* **1988**, *21*, 1241. (b) Ercolani, G.; Mencarelli, P. *J. Chem. Soc., Perkin Trans. 2* **1989**, 187.

$Br(CH_2)_8CO_2^-$ in 99% Me_2SO,[19] for which it was found that $k_{dim} = 0.45k_{inter}$. If one assumes that similar figures apply as well to 11-bromoundecanoate in DMF, the resulting k_{intra}/k_{dim} ratio of 1.3×10^{-2} M is translated by means of eq 2 into a value of 84% for the maximum yield of the monomeric ring, the rest of the mass balance being accounted for by the cyclic dimer and only to a limited extent by higher order polymers. The latter yield value compares remarkably well with the 83 ± 1% yield of 1 actually observed in the absence of added salts, i.e., when the Bu_4N^+ ion accompanying the added base was the sole counterion. Small amounts of the dimer were occasionally detected by GLC, but no effort was made to quantify them.

Table II shows that there is a general tendency for the lactone yields to decrease (i) with increasing added salt concentration and (ii) with decreasing cation radius. Whereas the yields obtained in the presence of the lowest concentration of the larger cations approach very closely the limiting value of 84%, a dramatic drop in yield is seen with Li^+. We note that replacement of perchlorate for bromide as the counterion has no effect on yields, which is in agreement with the idea that alkali-metal bromides and perchlorates behave as strong electrolytes in DMF.[9,11]

The picture that emerges from Table II is fully consistent with our recent analysis of ion-pairing effects on the kinetics of lactonization,[11] where it was shown that the association tendency with carboxylate ions decreases in the order $Li^+ > Na^+ > K^+ > Cs^+ > R_4N^+$.[20] The reaction time being equal, the yield decrease brought about by increasing concentrations of added salt is a clear consequence of the adverse effect of cation pairing on the reactivity of carboxylate, i.e., $k_{ip} \ll k_i$ (Scheme I). That the yield-decreasing effect is simply due to a decrease of the conversion of the ω-bromoalkanoate reactant into products, caused by a lower concentration of reactive free carboxylate brought about by extensive association with the smaller metal ions, and *not* to a variation of the k_{intra}/k_{inter} ratio, is clearly shown by the experiments carried out in the presence of 0.2 M LiBr. The insignificant yield of less than 1% obtained after 90 min becomes a 52% yield on increasing the reaction time up to 6 days. This now equals the yield obtained in the presence of 0.2 M $CsClO_4$ after 90 min. Hence, lithium 11-bromoundecanoate after 90 min was almost unreacted. Judging from the behavior of 15-bromopentadecanoate, the rate-inhibiting effect of 0.2 M $LiClO_4$ is roughly 2 orders of magnitude larger than that of 0.2 M $CsClO_4$.[11] This again indicates that, at least under homogeneous conditions, there is a close correspondence between kinetic and preparative experiments and conclusively demonstrates that cesium ion exerts no *special* effect on the competition between macrocyclization and polymerization.

Macrocyclization under Heterogeneous Conditions. As is usual in preparative work,[2,10] lactonization of 11-bromoundecanoic acid was also carried out by treating a solution of the bromo acid in DMF with an excess of alkali-metal carbonate, which is sparingly soluble in the given solvent. The yields of 11-undecanolide obtained after a fixed amount of time (2 h at 80 °C) are listed in Table III. It is apparent that the overall picture is strictly comparable to that obtained under homogeneous conditions in the presence of the lowest concentration of added salts (Table II, $[MX] = 8 \times 10^{-3}$), showing that the presence of insoluble alkali-metal carbonate has no major effect on the outcome of the lactonization process. These results are consistent with our previous finding[17] that acid–base reaction of ω-bromoalkanoic acids in Me_2SO with solid K_2CO_3 is fast and virtually quantitative and that subsequent cyclization of the ω-bromoalkanoates thereby formed is unaffected by the presence of the solid material.

Conclusions. The results of the preparative experiments reported in this paper are in remarkably good agreement both with the kinetic principles underlying macrocyclization phenomena[14] and with the well-known adverse effect of ion pairing on the reactivity of anionic nucleophiles in S_N2 reactions.[21] The increasingly adverse effect on lactone yields found on increasing added salt concentration under homogeneous conditions, as well as the yield-depressing order among cations, namely, $Li^+ > Na^+ > K^+ > Cs^+ > R_4N^+$, are easily interpreted in terms of well-established ion-pairing effects on the reactivity of the carboxylate nucleophile.[11] No indication whatsoever is obtained that the counterion alters the cyclization/polymerization ratio in favor of the former. On practical grounds, whenever the chosen reaction time happens to be such that conversion of the bromo acid reactant into products is not complete, yields of lactone in the presence of Cs^+ are indeed higher than in the presence of the other alkali-metal ions, but differences with K^+ are in general small.

From a more general point of view, it is evident that in macrocyclization reactions of anionic nucleophiles there is no fundamental difference between cesium ion and its congeners, but simply a regular grading of reactivity easily attributable to cation size. It appears, therefore, that the belief in a special effect of cesium ion is based on erroneous extrapolation of data from synthetic experiments.[22]

Experimental Section

Details on the kinetic method have been given previously.[11] The yields of lactone in the preparative experiments were reckoned gas chromatographically with tridecane as the internal standard. A pure sample of 11-undecanolide, available from earlier work,[23] was used for the determination of the response factor. Two typical experiments are given in detail below.

Homogeneous Lactonization. A solution of $Br(CH_2)_{10}CO_2H$ (50 mg; 0.189 mmol) and $CsClO_4$ (2.09 g; 9 mmol) in 45 mL of DMF (Erba RPE) was heated at 45 ± 2 °C. By syringe, 0.23 mL of a 0.85 M solution of $Bu_4N^+OH^-$ in MeOH (0.195 mmol) was added, and the resulting solution was stirred for 90 min. Brine was added along with the proper amount of tridecane, and the mixture was extracted with $CHCl_3$, washed, dried, and analyzed by GLC on a 5 m × 0.53 mm methyl silicone wide-bore column: a 52% yield of 11-undecanolide resulted.

Heterogeneous Lactonization. Cesium carbonate (56 mg; 0.172 mmol) was added to a solution of $Br(CH_2)_{10}CO_2H$ (12 mg; 4.5×10^{-2} mmol) in 21 mL of DMF (Erba RPE). The resulting suspension was vigorously stirred at 80 ± 2 °C for 2 h. After workup as above, an 82% yield of 11-undecanolide was obtained gas chromatographically.

Acknowledgment. Financial support by the Italian MPI is gratefully acknowledged.

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(19) Galli, C.; Mandolini, L. *J. Chem. Soc., Perkin Trans. 2* 1977, 443.

(20) Irregular behavior, namely, $Na^+ > Li^+$, may occur in some cases; see ref 11.

(21) Gordon, J. E. *The Organic Chemistry of Electrolyte Solutions*; Wiley: New York, 1975.

(22) Talma, A. G.; Jouin, P.; De Vries, J. G.; Troostwijk, C. B.; Werumeus Buning, G. H.; Waninge, J. K.; Visscher, J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 3981. In particular, see footnote 39.

(23) Galli, C.; Mandolini, L. *Org. Synth.* **1978**, *58*, 98; *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 698.