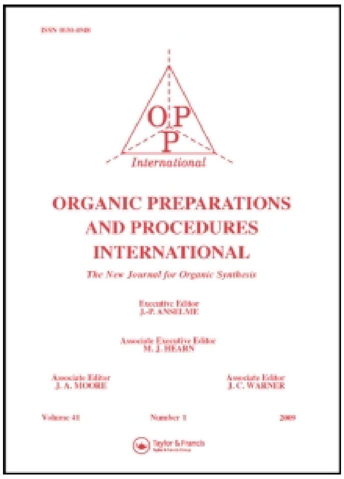

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Galli, Carlo(1992) '"CESIUM ION EFFECT" AND MACROCYCLIZATION. A CRITICAL REVIEW', Organic Preparations and Procedures International, 24: 3, 285 — 307
To link to this Article: DOI: 10.1080/00304949209355891
URL: http://dx.doi.org/10.1080/00304949209355891

ORGANIC PREPARATIONS AND PROCEDURES INT., 24 (3), 285-307 (1992)

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INTRODUCTION

The purpose of this review is to discuss critically the results that have been associated with use of a cesium salt in synthesis. These results, which have been referred to as the "cesium ion effect",[1,2] are not exceptional in their own right but are instead a simple manifestation of well understood physico-chemical effects; it is not necessary to invent and believe in a "new" effect. These experimental results, typically, arise from nucleophilic displacement reactions run in dipolar aprotic solvents such as dimethylformamide (DMF) with anionic nucleophiles, generated *in situ* from the parent acid by an

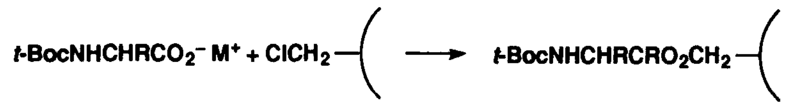
$$\mathrm{RXH} + \mathrm{R'Y} \xrightarrow{M_2CO_3} \mathrm{RXR'} + \mathrm{HY} \qquad (1)$$

$$X = CO_2,\ O,\ S \qquad Y = \text{Halogen, Tos}$$

alkali metal (M) carbonate as the heterogeneous base. When the counterion of carbonate is cesium, higher yields of product are claimed to result, in comparison to the yields with the other alkali metal (Li,Na,K,Rb) carbonates. Intramolecular versions of these S_N2 processes have been widely exploited in the literature[1] for the formation of cyclic compounds, and this is why the "cesium ion effect" and macrocyclizations are interwoven. The synthetic usefulness of a procedure which increases the yield of products is not questioned, provided that such an increase is *really* significant! What is questionable in the case of Cs_2CO_3 is the interpretation that has been given to the phenomenon itself. Although some authors have attributed the phenomenon to *special* properties of cesium ion,[2,3] the purpose of this review is to show that there is nothing in cesium ion to deserve an exceptional explanation.

I. HISTORICAL BACKGROUND

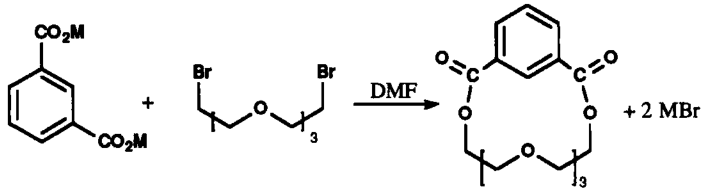
In 1973, Gisin reported an efficient S_N2 esterification procedure of salts of N-protected amino acids with chloromethylated polystyrene,[4] which resulted in an improvement of the Merrifield peptide synthesis.[5] A dependence of the esterification efficiency on the size of the counterion M^+ was found



$$t\text{-BocNHCHRCO}_2^-\,M^+ + ClCH_2\text{-}\big(\longrightarrow t\text{-BocNHCHRCRO}_2CH_2\text{-}\big(\qquad (2)$$

among the alkali metal ions. Indeed, cesium carboxylate gave the highest incorporation of amino acid into the resin, after a fixed reaction time in DMF; the incorporation with Cs^+ was more than one order of magnitude greater than for lithium and nearly double that of the potassium ion. Gisin postulated[4] that association of a carboxylate ion and a metal cation into *ion pairs* in DMF would be expected to be lower the larger the cation, due to well-known electrostatic considerations.[6] "Since the carboxylate rather than the ion pair is the nucleophile that displaces the chloride..." (in Eq. 2) "... a high degree of dissociation will result in a high concentration of the reacting species and consequently increase the reaction rate".[4]

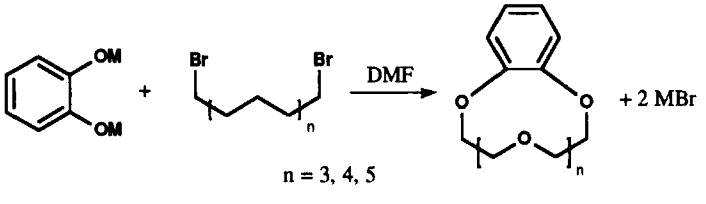
The method of Gisin was adopted by Kellogg and coworkers[7,8] to prepare crown-ethers. In the first paper,[7] Kellogg underscored the unique effect of Cs^+ compared with Na^+, K^+ and Rb^+ and



(3)

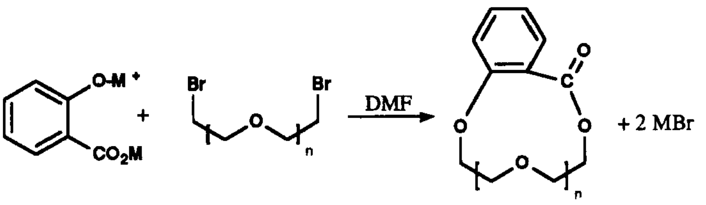
M^+ (yield, %): Cs^+ (75), Rb^+(75), K^+(15), Na^+(5)

suggested that Cs^+ acted as a *template* in early stages of ring closure. This was indeed a sensible explanation, since a polyoxyethylene chain capable of complexing metal ions was involved in the ring formation. In the second paper,[8] when the nucleophile was a catecholate (Eq. 4), no differences in



(4)

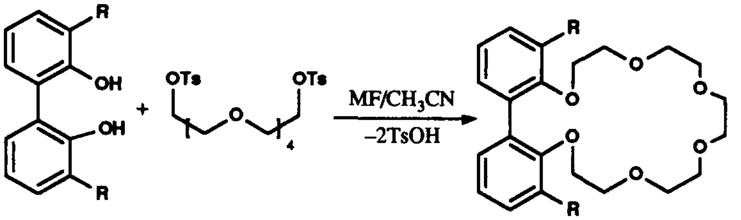
product yields among the alkali metal cations were noted. Only a slight improvement was observed with Cs^+ compared to K^+ in the case of salicylate anion (Eq. 5).[8]



(5)

n =		3	4	5
Cs^+	(yield,%):	36	54	68
K^+	(yield,%):	36	12	54

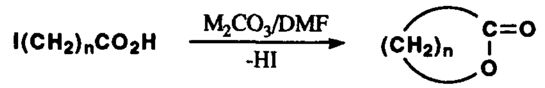
Reinhoudt *et al.* subsequently reported the use of fluoride ion in acetonitrile for the deprotonation of aromatic diols to form crown ethers by the cyclization of ditosylates of oligoethylene glycols. Modest improvements in yields were observed with CsF compared with RbF and KF. No reaction occurred with the smaller LiF and NaF, and very poor results were obtained with the very large Bu_4NF, confirming the necessity for an optimum fit between size of the cation and cavity of the ring being formed, typical of the "template effect". The different *solubility* of CsF, RbF and KF in CH_3CN



(6)

(KF in particular is poorly soluble[10]) was likely superimposed on the template effect, and led to the observed overall results, as the authors pointed out.[9] Therefore, up to this juncture, in synthetic procedures employing cesium salts, no special effects had appeared that could not be explained by known phenomena, such as ionpairing or the template effect.

A watershed paper[2] described an intramolecular esterification of an ω-iodo- or ω-bromoalkanoic acid under mild conditions in DMF with M_2CO_3. The yields of macrolides were the highest for



(7)

Cs_2CO_3, the lactonization efficiency being dependent on the size of the cation M, with Li_2CO_3 leading to practically no reaction. An important point is that a *fixed* reaction time was adopted. The argument correctly advanced by the authors was that a template effect could not be invoked to explain the yield/cation relationship, because a simple polymethylene chain was involved in this case (Eq. 7). The authors[2] proposed that carboxylate anions in DMF are associated with cations in ion pairs or even ion triplets. They further suggested that over the large and polarizable surface of cesium ion, which is

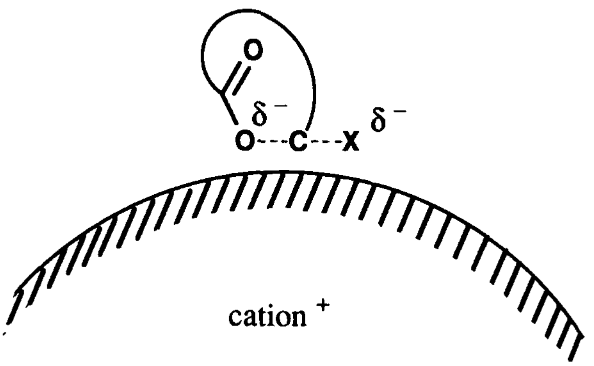


Fig. 1

Suggested Origin of the "cesium ion Effect"
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endowed with a low charge/surface ratio, the associated -halocarboxylate would have i) an intrinsic higher reactivity and ii) more chances to bite its own tail rather than the tail of another halocarboxylate (Fig. 1). Accordingly, the carboxylate associated with Cs^+ would have a *lesser* tendency to undergo intermolecular (i.e. polymerization) than intramolecular reaction: this would explain the ability of cesium ion to *promote* cyclization.

This explanation, as depicted in Fig. 1, is subject to criticism. In fact, the ionic radius of Cs^+ (1.6 Å) is not very different from that of the oxygen in $-CO_2^-$ (1.40 Å), and is indeed smaller than those of I^- or Br^- (2.15 and 1.95 Å, respectively). Therefore, Fig. 1 is not drawn to scale. But even if the picture were in scale, there is no reason to believe that cesium carboxylate would preferentially "bite" its own tail, which is uncharged and has no reason to be complexed over the cesium surface, in preference to the tail of another adjacent halocarboxylate molecule. Hence, the suggested higher *intra*- vs. *intermolecular* reactivity of a cesium haloalkanoate appears unfounded.

This and previous criticisms[11] notwithstanding, the explanation of Fig. 1 was appealing. Other papers described the successful use of cesium carbonate in synthesis.[12–18] Chemical catalogues began to add to the entry "cesium carbonate" a short comment, recommending it for macrocyclizations with quotations from the leading papers.[2,7,8] Thus the use of Cs_2CO_3 in synthesis became a commercial fact. Although it is ten times more expensive than K_2CO_3, it had the allure of novelty and success!

Other authors have also given credit to the "cesium ion effect".[1,19,20] The use of Cs_2CO_3 allowed improvement in the yields in the cyclization to thiacyclophanes.[21,22] However, comparison was made between a 65% yield of a ring obtained with Cs_2CO_3 in DMF with a 9.4% yield of the same ring obtained under conditions which are *not* comparable, *i. e.*, KOH in 1-butanol. According to the authors, this dramatic difference in yield is certainly due to the "cesium ion effect":[23] no mention of the very different nature of the two solvents was made. The successful synthesis of various thioethers is, according to this view, a manifestation of the tendency of Cs^+ to *favor* cyclization over polymerization. Even more disturbing, cesium was reported[19,21,24] to assist *specifically* the synthesis of *strained* rings. Other authors have promoted the effectiveness of Cs^+ for the synthesis of macrorings, based on a comparison of yields obtained with Cs_2CO_3 in DMF with respect to those with KOH in EtOH.[25,26] Because of such non-critical but vigorous support, the use of cesium salts in synthesis, and particularly in macrocyclizations, has become a standard procedure.[27,28] It is used without question.[29,33] Comparison with the effect of other bases, that could work as well, has been neglected. Whenever an explanation is required, reference to Fig. 1 is made.[34] In addition, experimentally unsupported statements such as "cesium probably promotes this reaction by forming weak ion pairs with RS^- anions, which would make them exceptionally nucleophilic",[35] and "benefit was taken from the ability of cesium ion to gather fragments for S_N2 reactions"[36] continue to appear. These statements maintain the belief of the nearly magical properties of cesium ion.

II. THE SEARCH FOR A SPECIAL PROPERTY OF CESIUM SALTS

In the past twenty years, several studies have appeared where solution properties of alkali metal salts have been compared. Free energies of transfer of alkali metal ions from H_2O to neat solvents such as MeOH, EtOH, PrOH,[37] or to solvent mixtures such as MeOH-H_2O, *t*-BuOH-H_2O, acetone-H_2O, dioxane-H_2O,[38] CH_2Cl_2-H_2O,[39] show a simple, nearly linear, grading of the G_{trans} value with cation size. A few general conclusions can then be reached. The smaller the size of an ion, the more pronounced the solvation. The structure of the solvation shell is more organized in protic than in aprotic solvents. The behavior of cesium is perfectly consistent with that of other alkali metal ions.

Conductance measurements for alkali-metal halides in both dipolar and non polar solvents, show that ion-pairing is important even at modest concentrations. *Complex* dependence of the extent of ion-pairing among the alkali metal cations may be observed, depending on the structure of the solvent. In 2-methoxyethanol[40] and in mixtures of 1,2-dimethoxyethane-H_2O,[41] for example, the strength of the association follows the trend Li>Na≈K<Rb<Cs, which is the result of competition of opposing factors, such as Lewis acid-base or electrostatic interactions. More linear trends are observed with alkali-metal halides in tetramethylurea,[42] in EtOH[43] and in N-methylformamide,[44] or with alkali metal nitrates in dimethylsulfoxide (DMSO).[45] In these studies, no singular feature appears associated with Cs^+; in some cases anomalies were found, but they occurred with lithium ion.[45] Other studies[46–51] upon ion-pairing have confirmed some general principles:[6,52,53]

i) association between cation and anion is stronger as the size of the ions decreases

ii) the lower the dielectric constant of the solvent, the stronger the ion-pairing, at least for solvents of similar kind

iii) there is a simple gradation of the association behavior within the alkali-metal family.

Inversions in the association strength may be observed, particularly in connection with delocalized anions,[48,54] as resulting from a competition between affinity for the solvent or the anion, but these are more likely to occur between Li^+ and Na^+ than between K^+, Rb^+, and Cs^+, the last three always being very similar. For example,[55] a ^{13}C NMR investigation of the association in ethereal solvents between alkali metal cations and delocalized carbanions, such as those from triphenylmethane, diphenylmethane or fluorene, indicated the presence of solvent-separated ion pairs with Li^+ and Na^+, but tight ion pairs with K^+, Rb^+, and Cs^+.

Solubility is less easily rationalized and less well documented. Its effects upon reactivity may be significant. Potassium salts are often less soluble than the corresponding sodium or cesium salts,[10,56] particularly in DMF or CH_3CN. Cesium carbonate is the most soluble of the congeners in dipolar aprotic solvents.[3,57] These experimental facts might be related with the lattice energy of the solids.[58] The order of solvating ability with cesium salts is HMPT > DMSO > DMF > CH_3CN.[59] It is not odd, therefore, that the "cesium ion effect" appears more pronounced in DMF than in DMSO or HMPT. Understandable[10] is also the fact that K_2CO_3 in DMF sometimes provides less satisfactory results in comparison to Cs_2CO_3.[2,3,12,22]

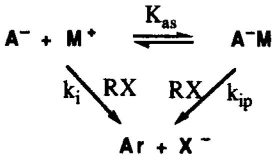
In conclusion, the available experimental data about the solution behavior of the alkali metal cations point to a *regular* variation of their properties.

III. DISCUSSION

A more thorough examination of the origin of the effects associated with the use of cesium ion must be subdivided into three parts: 1) intermolecular 2) cyclization and 3) templatedriven intramolecular reactions.

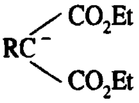
1. Intermolecular Reactions

Initially, Gisin advanced an explanation for the higher yields obtained with cesium ion that is still convincing.[4] The carboxylate ion but in more general terms the anion,[4] would be associated with the cation to form ion pairs, while the reactive form would be the "free" species. According to Scheme 1, the free ion and the associated form are in an equilibrium controlled by the association constant (K_{as}).[52] The intermolecular S_N2 esterification of Gisin[4] would be a case where the reactivity of the free ion is much higher than that of the ion pair, i. e. $k_i >> k_{ip}$. Since it is reasonable to assume the association with Li^+ to be the strongest,[50] the amount of *reactive* free species would be the lowest with this cation, and the intermolecular reaction with an electrophilic species (RX) would be the most retarded.[52–54] The opposite would be true with cesium ion. If the reaction time is the *same*, the fastest intermolecular process, i. e. the one with Cs^+, would provide the highest yield, as it was indeed found.[2–4,12] The sound rationalization of Gisin[4] was however qualitative. It was not supported by specific kinetic data, but made reference to the general concepts about ion-pairing which have been discussed above.[52,53] We have carried out a kinetic determination of the effect of ion-pairing upon the S_N2 reactivity of a carboxylate anion in DMSO and in DMF.[54] This investigation followed early studies where the ion-pairing of other nucleophiles had been examined with consistent results.[49,50,60,61] Our approach allowed the determination of the reactivity of the free ion and the association constant.[54] It was found[49,50] that ion-pairing of a nucleophile is rate depressing (not rate accelerating!), to an extent closely reflecting the strength of the association of the cation (Table 1). This was equally true for the carboxylate anion[54] which showed detectable incursion of ion-pairing in both DMSO and DMF at concentrations as low as 10^{-2} M. As expected, the extent of ion-pairing was stronger with Li^+ and weaker with Cs^+ (the others being intermediate) and slightly more pronounced in DMF than in DMSO, in agreement with their dielectric constants (37 and 47, respectively). Another important point is that contribution to the overall reactivity of the carboxylate from the associated species turned out to be small, in comparison with the contribution from the free ion, even under conditions where most of the carboxylate ions were in the associated form.[54] In this fashion, experimental support to Gisin's assumptions and rationalization[4] was provided. Ion-pairing of AcO^-K^+ in DMF and in other solvents



Scheme 1

TABLE 1. Effect of Ion-pairing on Nucleophilic Reactivity in DMSO at 25°.

Nucleophile	Ion	log K_{as}	k_{ip}/k_i	% Free Ion (at 0.1 M)	% Reactivity *via* Free Ion
ArO^-	Li^+	3.3	1×10^{-5}	1	99
	K^+	1.6	3×10^{-2}	36	94
	Li^+	5.1	1×10^{-4}	0.02	60
	K^+	2.3	1×10^{-1}	10	44
RCO_2^-	Li^+	2.1	1×10^{-1}	18	67
	K^+	1.7	3×10^{-1}	34	61

has also been reported recently.[56] In 1987, researchers[3] attempted to adduce evidence of ion-pairing of cesium propanoate in DMSO and in DMF by means of ^{133}Cs NMR. The narrow concentration range studied did not allow a full appreciation of the phenomenon. In fact, it was concluded that, at the concentrations employed, cesium propanoate was essentially present as a free anion, which indeed is the reactive species in the nucleophilic substitution. Although this conclusion is substantially wrong, since cation-anion association is instead significant under those conditions,[54] the resulting view was quite different from the original one[2,13] of a "tight ion pair" endowed with a *peculiar* reactivity, and resembled more closely Gisin's explanation.[4] Still, the authors concluded that the effectiveness of cesium alkanoates derives from the fact that"...the carboxylates are essentially free and *highly reactive*".[3] Such a high reactivity would also contribute favorably in macrocyclization processes.[3]

We will deal next with macrocyclization, but cannot refrain from noting that the above mentioned *high reactivity* is misleading. It might lead to such unsupported statements as the "exceptional nucleophilicity",[35] or provoke the theoretical investigation by Blum.[62] According to the latter study, the "cesium ion effect" is due to a peculiar potential surface surrounding cesium, but *not* the other cations; the reactants of the S_N2 process are suitably situated in a close arrangement and therefore react efficiently.[62] A more precise statement, instead of "high reactivity", would be that *decrease* of the extent of ion-pairing, in going from Li^+ to Cs^+, makes the reactivity of the nucleophile gradually approach the *limiting* reactivity of the free ion. Such a reactivity is remarkable simply because the process is performed in a dipolar aprotic solvent (DMF or DMSO); indeed it is well known that dipolar aprotic solvents are far better than the protic ones for displacements involving anionic nucleophiles.[53,63,64] Therefore, those yield effects[23,25] are simply the consequence of the higher reactivity of a naked anion in DMF or CH_3CN, as compared with the reactivity of the same anion when heavily solvated by hydrogen bonds in a protic solvent.[65]

A final comment concerns the heterogeneity of the medium. In the early experiments,[4,7,8] the reactive salts were preformed and then added to the solution. Subsequently, a suspension of the alkali metal carbonates,[2] which are sparingly soluble in the dipolar aprotic solvents,[57,66] was used to generate the anion *in situ* from the parent acid. Although we have verified that the heterogeneity of the medium does not modify the nucleophilicity of the species,[67] the efficiency of the acidbase conversion is probably affected by the different solubility of the carbonates. In fact, a more soluble carbonate will ensure a higher amount of base *in solution* for the deprotonation. Since cesium carbonate is the most soluble carbonate of the series,[57] this, along with the lower incidence of ionpairing with Cs^+, contributes to a higher conversion to product within a fixed time.

2. Cyclization Reactions

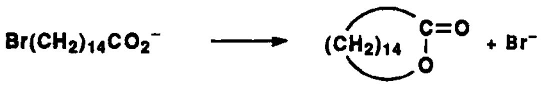
The cyclization of an α,ω-bifunctional precursor (k_{intra}, Eq. 8) in principle suffers from intermolecular competition (k_{inter}), leading to oligomers (both linear and cyclic) and to higher polymers (Eq. 9).[68] The ratio k_{intra}/k_{inter} is known as the effective molarity (EM), and represents the tendency of

(8)

$$2\ X(CH_2)_nY^- \xrightarrow{k_{inter}} X(CH_2)_nY(CH)_nY^- + X^- \qquad (9)$$

that ring to form.[68] The higher the EM, the more easily the ring will be formed. The EM has the dimension of a concentration. Its physical meaning[68] is the concentration of monomer at which cyclization (a monomolecular process) and polymerization (a bimolecular process) would proceed with the same rate. Strong as medium effects can be on the reactivity of a functional group, they are in general felt to the same extent *both* in the intra- and in the intermolecular processes (at least for n values ≥ 4); consequently, the EM results remain rather unaffected.[69,70]

The inferred ability of cesium to direct the reaction in an intramolecular fashion[3] or to gather fragments for intramolecular S_N2 reactions,[36] would require the association of Cs^+ with the reactive species and an EM of the associated species higher than that of the unassociated one. These two points were not addressed by early investigators.[2] We have carried out a kinetic investigation of the effect of ion-pairing upon the cyclization of $Br(CH_2)_{14}CO_2^-$ in DMF,[54,71] as a model of a macrolactonization



(10)

akin to those of Kruizinga and Kellogg.[2] As Fig.2 shows, the addition of increasing amounts of an inert (M^+Br^-) salt always has a rate depressing effect upon the intramolecular reactivity of $Br(CH_2)_{14}CO_2^-NR_4^+$, being stronger with Li^+ and weaker with Cs^+; R_4N^+ showed negligible rate-depressing ion pairing. Our kinetic analysis shows that the *free ion* is the reactive species, the reactivity of the ion-paired species being negligible or nearly so. We have also demonstrated that the intra-and the intermolecular reactions (Eqs. 8 and 9) of this substrate are affected equally by ion-pairing, as shown by the fact that the EM is insensitive to the nature of the counterion (Table 2).[71] This is exactly what is expected for reactions proceeding *via* the *free ion*: the complexity of the nature of the solution[62] will be irrelevant to the intra- *vs.* intermolecular behavior of the free ion. Equally irrelevant will be the structure of the associated form (see Fig. 1),[2] since it does not give a kinetic contribution. This is true even though the latter associated form is the predominant species, because the chemical transformation at hand is mainly due to small amounts of unassociated species present in the equilibrium of Scheme 1. Thus, the suggested higher reactivity of nucleophiles associated with cesium,[2,12,13,35] and its capacity to favor intramolecular reactions,[1,3,35] are unfounded.

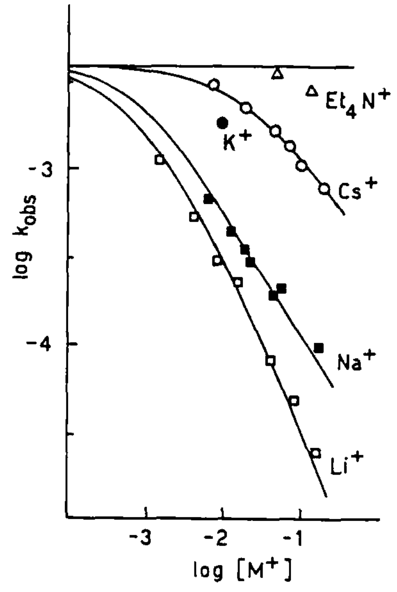


Fig. 2

Effect of Added Salts on the Rate of Lactonization of $Br(CH_2)_{14}CO_2^-$ in DMF at 45°. The horizontal line represents the reactivity of the free ion, the points are experimental and the curves are calculated (see ref 54).

TABLE 2. Effect of Ion-pairing with M^+ on the Intra- and Intermolecular Reactivity of RCO_2^- in DMF at 45°

M^+(0.05 M	$k_{intra}(s^{-1})^a$	$k_{inter}(M^{-1}s^{-1})^b$	EM(M)^c
Et_4N^+	4.3×10^{-3}	17×10^{-2}	2.5×10^{-2}
Cs^+	1.3×10^{-3}	4.8×10^{-2}	2.7×10^{-2}
Na^+	0.24×10^{-3}	1.0×10^{-2}	2.4×10^{-2}

a) Lactonization of $Br(CH_2)_{14}CO_2^-R_4N^+$. b) Measured on the model reaction between $CH_3(CH_2)_4CO_2^-R_4N^+$ and BuBr. c) Calculated as k_{intra}/k_{inter}.

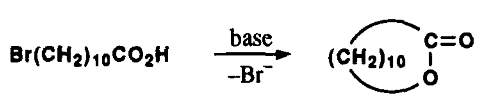
Still, the yields obtained in cyclization with Cs_2CO_3 are often better. Again, this is due to the fact that the nucleophilic processes (*both* intra- *and* intermolecular) are faster with Cs_2CO_3, due to the lower incidence of ion-pairing.[54,71] When the chosen *reaction time* is equal, lower yields of cyclic compounds with the other cations are the result of *incomplete* conversion of reactant into product, as illustrated[71] in Table 3. In the lactonization (Eq. 11) run under conditions similar to those of Kellogg[2] and under strong ion-pairing, the yield using cesium counterion (52%) was by far greater than with lithium (<1%) after the same time (90 min). However, on increasing the reaction time to 6 days, the yield with Li^+ became 52%, equal to that with Cs^+. Thus, after 90 min the lithium carboxylate was nearly *unreacted*; however, with Bu_4N^+, whose pairing with carboxylates is negligible, the yield was even *higher* (63%) than that with Cs^+, confirming a modest but appreciable incursion of ion-pairing and therefore of retardation even with Cs^+.

TABLE 3. Synthetic Consequences of Ion-pairing of a Nucleophile with Purposedly Added M^+. Effect on the Yield of 11-Undecanolide from $Br(CH_2)_{10}CO_2^-$ in DMF at 45°[a]

M^+ (0.2 M)	Reaction Time (hrs)	Yield of Lactone (%)
Bu_4N^+	1.5	63
Cs^+	1.5	52
Na^+	1.5	11
Li^+	1.5	<1
Li^+	150	52

a) At a $4x10^{-3}$ M initial concentration of $Br(CH_2)_{10}CO_2^- NR_4^+$, prepared by neutralization of the bromoacid with $Bu_4N^+ OH^-$.

Also significant is a study (Table 4) of the effect of the solvent and of the nature of the base upon the lactonization of 11-bromoundecanoic acid (Eq. 11).[71,72] First, the expected much higher



(11)

efficiency of the dipolar aprotic solvents (DMF, DMSO, CH_3CN, N-methylpyrrolidone) with respect to ethanol in this cyclization was confirmed. Potassium carbonate in DMSO is almost as satisfactory as Cs_2CO_3 in DMF as previously demonstrated,[67,73-76] whereas in 2-butanone, the yield with Cs_2CO_3 was *lower* than with K_2CO_3.[72] Schill had similarly obtained better results with Na_2CO_3 than with K_2CO_3 in isopentanol.[77] In other examples,[75,76] K_2CO_3 gave better results than Cs_2CO_3 in DMF. This confirms[36,76] that Cs_2CO_3 is not *always* the best choice, but that a delicate balance of various factors (e. g., solute-solvent interactions, ion-pairing, solubility of the anion) produce the most profitable combination in different cases.[58,78] The relevance of ion-pairing upon reactivity comes out neatly in 2-butanone (Table 4).[72] Addition of a substantial amount of CTABr (cetyltrimethylammonium bromide) to the suspension of K_2CO_3 improves the yield of lactone from 22 to 55%.[72] This is due to the fact that, owing to mass effect,[56] the large and weakly-associating R_4N^+ cation[53,56,66] replaces the strongerassociating K^+ ion, thus "restoring" the nucleophilic reactivity of the carboxylate. Finally, the relevance of the solubility of the base for the efficiency of the deprotonation[72] becomes evident from the experiment conducted in benzene. Lactonization with K_2CO_3 or Cs_2CO_3, which do not dissolve to any great extent in benzene, were unsuccessful. Use of the base $Bu_4N^+OH^-$, featuring a large lipophilic cation, instead provided an efficient conversion of the bromoacid into bromocarboxylate.

TABLE 4. Effect of the Solvent and of the Base on the Yield of 11-Undecanolide from $Br(CH_2)_{10}CO_2H$.[a]

Solvent	ReactionTemp.(°C)	Base[b]	Yield (%)
DMSO	80	K_2CO_3	76±2
		Cs_2CO_3	77±1
DMF	80	K_2CO_3	80±2
		Cs_2CO_3	82±2
		Li_2CO_3	22±1
CH_3CN	81[c]	K_2CO_3	70±1
NMP[d]	80	K_2CO_3	67±2
EtOH	79[c]	K_2CO_3	3±1
2-butanone	80[c]	K_2CO_3	22±1
		Cs_2CO_3	9±1
		K_2CO_3[e]	55±1
benzene	78[c]	K_2CO_3	0.1
		$Bu_4N^+OH^-$[f]	74±2

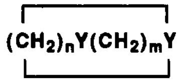
a) Initial concentration of $Br(CH_2)_{10}CO_2H$: 2.2×10^{-3} M. Reaction time: 2 hrs. b) Heterogeneous and in excess. c) At the boiling point. d) N-methylpyrrolidone. e) In the presence of [CTABr] 7.5×10^{-3} (see text). f) Soluble and in equimolar amount.

At this point the reactivity of the latter anion, presumably loosely associated with the bulky cation, in benzene, was not much different from that of the more "celebrated" dipolar aprotic solvents, as the yield of lactone (74%) shows.[20]

The general requirement to be met in a cyclization is a *low concentration* of the monomer (in Eqs.8 and 9), which will discourage the incursion of intermolecular side-reactions.[68] The lower the EM, the more stringent is this requirement: this is the case for the macro-rings or, even more so, for the mediummembered ones.[79] Two approaches have been employed[67,68] to meet the above requirement. In the *batch-wise* method (see Table 4), the monomer is added at the beginning of the reaction to a large volume of solvent whereby suitable dilution is accomplished. To save solvent, the second method, known as the highdilution technique[80] or the *influx* procedure, features a slow addition of the monomer to a relatively small volume of solvent, resulting in a low stationary concentration of monomer. The slower the feed rate, the lower this stationary concentration and consequently the higher the yield. A kinetic analysis of the behavior and merits of these two cyclization procedures has been reported.[67] In particular, it was shown that in the latter procedure the rate of the building up of the stationary concentration of the reactive monomer and its absolute value, are a function not only of the EM, but also of the k_{intra}. Other parameters being equal, a higher k_{intra} value will cause the establishment of a lower stationary concentration, ensuring a higher yield of cyclized product. This point is not fully appreciated in the literature and sometimes comparison of yields is improperly done among experiments endowed with different[81] (or not even specified![33]) feed rates of monomer. Another point which is relevant to the "cesium ion effect" is that, whenever a cyclization is run under influx conditions with Cs_2CO_3 in DMF, slightly higher yields of cyclic product are to be expected; this is due to the above effects which make higher the k_{intra} value with Cs^+ than with the other alkali-metal cations. Consequently, the dependence of ring-yield *vs.* cation-size may be *more* pronounced in favor of Cs^+ ion, with respect to the case of the batch-wise procedure. In the latter case, yields are only affected by the EM values,[67] which are independent of ion-pairing.[70,71] Once again it is emphasized that with both procedures yields *vs.* cation-size effects are exaggerated by incomplete conversions (i. e. when the reaction time is chosen on the basis of the faster process, the one with cesium).

We have seen so far the cyclization of α,ω-*bi*functional compounds, i. e. $X(CH_2)_nY^-$. However, cyclization can also occur by joining two *homo*functional pieces together. This approach has

$$\underset{\mathbf{1}}{X(CH_2)_nX} + \underset{\mathbf{2}}{^-Y(CH_2)_mY^-} \xrightarrow{-X^-} \underset{\mathbf{3}}{X(CH_2)_nY(CH_2)_mY^-} \qquad (12)$$



$$\underset{\mathbf{3}}{X(CH_2)_nY(CH_2)_mY^-} \xrightarrow{-X^-} (CH_2)_nY(CH_2)_mY \qquad (13)$$

$$\underset{\mathbf{3}}{X(CH_2)_nY(CH_2)_mY^-} \xrightarrow{-X^-} X(CH_2)_nY(CH_2)_mY(CH_2)_nY(CH_2)_mY^- \qquad (14)$$

$$\underset{\mathbf{3}}{X(CH_2)_nY(CH_2)_mY^-} + \underset{\mathbf{1}}{X(CH_2)_nX} \xrightarrow{-X^-} X(CH_2)_nY(CH_2)_mY(CH_2)_nX \qquad (15)$$

been referred to by Kellogg as a *two-stage* process,[3] which behaves somewhat differently from those previously described (Eqs. 8 and 9). The intermolecular stage (Eq. 12) is *favored* by a high concentration of the two species, while the intramolecular stage (Eq. 13) suffers, as usual, from intermolecular competition and is *disfavored* by a high concentration.

It has been stated[3] that cesium is used with special success in this type of macrocyclizations. This is because it would ensure a higher solubility to the doubly charged species **2**, increasing its reactivity toward **1** (in Eq. 12) with respect to the corresponding reaction between the monocharged anion **3** and **1** (Eq. 15). This would reduce the chance for oligomerization of **3** (in Eq. 15), with a net advantage for cyclization of **3** (Eq. 13). This rationalization is incomplete and unsatisfactory. The key competing path, which determines the effectiveness of the cyclization, is not (or not only) Eq. 15, but Eq. 14. Even if the explanation of a higher reactivity of the doubly charged anion were true, it would not affect the *inter*molecular reactivity of the monocharged anion **3** with another **3** (Eq. 14). Furthermore, it would imply an efficient formation of **3** in Eq. 12, thus leading to a *high* stationary concentration of **3**, and favoring polymerization over cyclization!

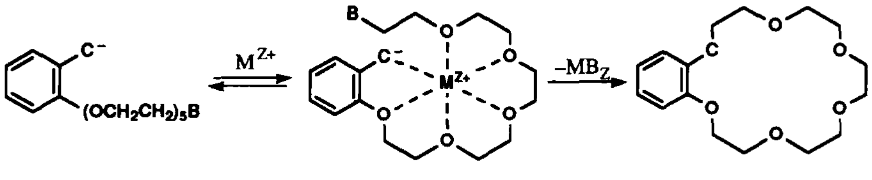
It is useful at this juncture to summarize a few points:

1. Nucleophilic processes occur more effectively in dipolar aprotic than in protic solvents;[53,63] this is true also for the intramolecular processes which afford cyclic products.
2. Association into ion pairs tends to reduce the reactivity of an ion;[82] the higher the dielectric constant of the solvent and the larger the dimensions of the ions, the lower the reduction in reactivity.
3. Solubility of the reactants is very important and may affect the reaction time considerably.[83]

On more practical grounds, Cs_2CO_3 in DMF represents a good base-solvent combination to perform a cyclization. The reasons for such an experimental finding have been widely commented in this review. Whether this deserves to be termed the "cesium ion effect" is left to the reader's judgment; the reasons behind it are certainly not those previously invoked.[1-3,13,25] It is safe to state that K_2CO_3 in DMSO is another good base-solvent combination, endowed with effectiveness akin to that of Cs_2CO_3 in DMF.[76] Even better results can be obtained by the use of the large tetraalkylamonium counterions, when this is practical, because the reduction of ion-pairing is enhanced.

3. Template-driven Intramolecular Reactions

Template cyclizations are processes where donor-acceptor interactions between lone pairs of heteroatoms (O, N) and a metal cation drive the folding of a suitable chain toward the ring-closure.[84,85]



Scheme 2

It is important to stress that the EM of a polyoxyethylene chain increases compared with that of a simple polymethylene chain of the same length. However, this is true *only* in the case of complexation by a cation, the effect upon the EM being the stronger (up to 3 powers of ten), the more the size of the cation fits in the ring being formed.[49]

Although the *template effect* is shown here for the cyclization of an α,ω-bifunctional precursor, it comes into play as well for a *two-stage* cyclization frequently used for the synthesis of crown-ether-type compounds (Eq. 6).[84,86] The template effect upon the EM generally leads to high yields of crown ethers; this is true even under concentrations where extensive polymerization could occur with a polymethylene-chain compound. High dilution is not required. Cesium ion improves cyclization yields.[19,34,86,87] However, *depending on the ring dimensions*, potassium or even sodium may turn out to be more profitable at times.[88] Therefore Cs^+ is only *one among several ions* capable of templation. The vague statement concerning a "pronounced cation effect on macrocyclization",[3] or other similar statements[9,31] praising a much higher than usual yield of a crown ether with Cs_2CO_3/DMF (Scheme

2), can be readily understood through the operation of a *different and specific* phenomenon, namely the "template effect". Indeed, Kellogg in his first paper[7] had pointed out the possible occurrence of such a precyclic complexation that, by favoring the intramolecular pathway, would explain the good yields of cyclic products.

Association of a cation with the anionic end group undergoing the intramolecular displacement is also present *along* with the association of the same cation with the oxygen atoms of the chain in the template arrangement.[49,85] The former cation-anion association, as was previosly demonstrated, is rate-depressing; the latter association is rate-accelerating, the better the cation/cavity fit. The overall effect on intramolecular reactivity is a compromise between these two factors. Since the "template effect" does not operate in the intermolecular competing process, while ion-pairing with the nucleophile is present both in the intra- and in the intermolecular processes, the EM will increase because of an overall rate enhancing effect upon the intramolecular reactivity, and a rate depressing effect upon the intermolecular reactivity.[49] The case of lithium ion is particularly significant. The extent of ionpairing with a nucleophile is the strongest, while its small ionic dimensions do not allow a significant templation.[49,88] As a result, the synthesis of a crown-ether by means of a nucleophilic intramolecular displacement with lithium counterion is disfavored by prevailing ion-pairing and affords unsatisfactory yields.[7,34,86] On the other hand, the synthesis of a macroring lacking the sufficient number of oxygen atoms, does not allow cation templation. Even in the presence of cations that would give a suitable fit to the dimension of the ring being formed, ion-pairing with the nucleophilic end-group is the only effect at play, leading to diminished reactivity; therefore, lower yields of cyclized product are obtained, being the lowest the smaller the cation.[49]

IV. EXPERIMENTAL SUGGESTIONS

Our approach to the synthesis of ring-compounds, both under *batch-wise* and under *influx* conditions, has been reported in previous papers.[67,73] The procedure described in *Organic Syntheses*[73] has particular relevance from the methodological point of view. The following are some general guidelines for the synthesis of ring-compounds.

First, since lactones are of interest as natural products,[89] some parameters of relevance to their synthesis are noted (Table 5). A thorough comparison of the synthetic advantages of the leading lactonization methods has recently been published;[76] the method making use of K_2CO_3 in DMSO,[73] was found to be the most efficient. We make here reference to a reaction (Eq. 11) featuring an alkanoic acid bearing a suitable leaving group (halogen, tosylate, mesylate) in the -position. The preferred solvents for this lactonization are DMSO and DMF.

If the batch-wise method is chosen, the EM of the ring is the only relevant parameter;[67,90] depending on the initial concentration of substrate, a higher or lower yield of lactone will result. Structural modifications of the simple polymethylene chain of the substrate may lead to significant EM changes (see oxygen,[69,88] *gem*-dimethyl,[68] rigid group effects[68,74]). Two numerical examples of theoretical yield[67] *vs.* initial concentration are given in Table 5. The theoretical yields are relative to quantitative conversion. The timing of the conversion varies according to the solvent or to the leaving group and the reaction times in DMSO with a bromide leaving group are given.[79] As the base, a stoichiometric amount of a $R_4N^+OH^-$ solution is recommended. Alternatively, K_2CO_3 or Cs_2CO_3 as heterogeneous bases are suggested. Details of a typical procedure follow (see Table 4).

Potassium carbonate (100 mg, 0.72 mmol) was added to a solution of $Br(CH_2)_{10}CO_2H$ *(42 mg, 0.16 mmol) in 70 ml of DMSO. The resulting suspension was vigorously stirred at 80 ±2 for 2 hrs. Brine was added, and the mixture extracted with* $CHCl_3$*, carefully washed to remove DMSO and dried. A 76% yield of 11-undecanolide was obtained, vs. a calculated*[67,71] *85% yield at this initial concentration (*$2.3x10^{-3}$ *M).*

TABLE 5. Simulated Lactonization Yields with the Batch-wise Procedure

Expected Values vs. Initial Concentrations

Ring Dimension	7	8	10	12	15	23
EM (*M*)[a]	$1.4x10^{-2}$	$1.4x10^{-3}$	$4.7x10^{-3}$	$1.5x10^{-2}$	$6.3x10^{-2}$	$8.4x10^{-2}$
react.time (min)	11	1035	310	95	23	17
yield(%) at $2x10^{-3}$M[b]	99	47	72	86	97	98
yield(%) at $2x10^{-2}$M[b]	88	12	26	48	77	82

a) A value of k_{inter}= 0.08 was taken. See ref 71 for the discussion. b) Initial concentration of bromoacid.

Because of the good solubility of the dipolar aprotic solvents in water, separation of phases during the work-up may be troublesome. It was useful to add at least an equal amount of brine to the reaction solution, and to extract three or more times with a solvent such as hexane or $CHCl_3$ or diethyl ether. Successful separation and near quantitative recovery (80% after *only one* extraction) result. In some cases,[91] a liquid/liquid continuous extractor was used when the solubility of the product in water was not negligible.

If the *influx* approach is chosen, the rate of feed (v_f) is the major parameter.[67,92] Table 6 gives two numerical cases. The v_f is reckoned as the molar amount of substrate times the total addition time (in sec) times the volume of solvent including one-half of the smaller volume of solvent where the substrate is dissolved. Either a dropping funnel or a motor-driven syringe may be used for the addition of the substrate solution. In the influx procedure, the absolute value of k_{intra} is sensitive to the temperature; as a consequence, the expected 11% yield of 8-octanolide at 50°, with a $v_f = 6x10^{-4}$ mol l^{-1} sec^{-1}, rises to 28% at 70°. Finally, an heterogeneous base is recommended, K_2CO_3 or Cs_2CO_3 in DMSO, and Cs_2CO_3 in DMF being the most convenient choices.[71,76] An example of a moderately "large scale" preparation of 11-undecanolide is provided.

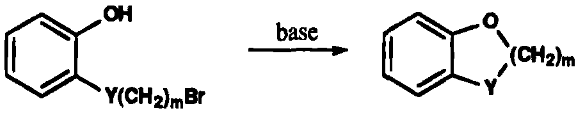
TABLE 6. Simulated Lactonization Yields with the Influx Procedure: Expected Values vs. Rates of Feed.

Ring Dimension	7	8	10	12	15	23
k_{intra}[a] (sec^{-1})	$1.1x10^{-2}$	$1.1x10^{-4}$	$3.7x10^{-4}$	$1.2x10^{-3}$	$5.0x10^{-3}$	$6.7x10^{-3}$
yield(%) at $v_f = 6x10^{-8}$ ($mol\ l^{-1}sec^{-1}$)	99	66	94	99	99	99
yield(%) at $v_f = 6x10^{-6}$ ($mol\ l^{-1}sec^{-1}$)	99	11	31	68	96	98

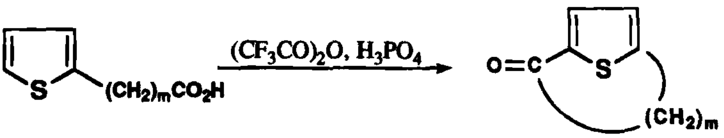
a) At 50° (see ref 79).


(ref. 91)

n = 7-13, 15


(ref. 93)

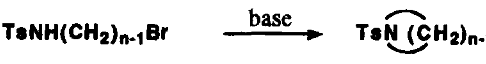
Y = CH_2 or O   m = 5-16, 24


(ref. 94)

m = 8, 9, 11, 13, 17


(ref. 95)

n = 6-13, 17, 21


(ref. 96)

n = 7-13, 17, 21

A $Br(CH_2)_{10}CO_2H$ (40 g, 0.15 mol) solution in 220 ml DMSO was added dropwise to a vigorously stirred suspension of K_2CO_3 (60 g, 0.43 mol) in 500 ml DMSO at 100 ±2°. The addition was over in 125 min ($v_f = 3.3x10^{-5}$ mol l^{-1} sec^{-1}). After an additional 10 min, the solution was cooled for 15 min, filtered using a Buchner to remove polymeric materials and poured into a separatory funnel containing brine and crushed ice. Extraction was carried out with petroleum ether (40-70°). After wash-

ing and drying (Na_2SO_4), removal of the solvent left 22 g of liquid (80%). Distillation (bp 125-127° at 16 Torr) gave 15.4 g of 11undecanolide (56% yield). The residue of the distillation was triturated with hexane and, on cooling, the 24-membered dilactone (4.3 g; 16% yield) was obtained (mp 71-72°).[73]

As a general conclusion, and according to the ring dimensions, a compromise must be reached between the yield and the need to minimize the volume of solvent or the addition time. Other ring-compounds which have been synthesized with success are summarized below.

Acknowledgment.- Financial support from the Italian MPI is hereby gratefully acknowledged.

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(Received January 17, 1992; in revised form April 21, 1992)