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Reactions of Carbonyl Compounds with Organic Derivatives of Alkali Metals and Hydride Reductants: the Effects of the Medium and the Cation

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The effects of the medium and the cation in the reactions of alkali metal salts of CH acids and hydride reductants with carbonyl compounds are analysed.
The bibliography includes 73 references.

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I. INTRODUCTION

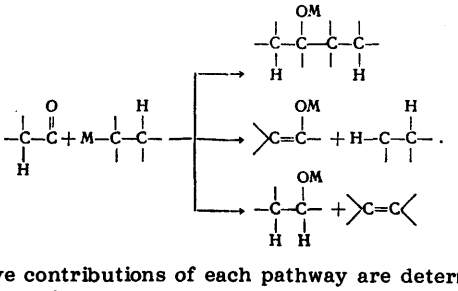
The reactions of carbonyl compounds with organometallic derivatives are widely used in synthetic organic chemistry as one of the main methods for the formation of the carbon–carbon bond. However, despite the enormous number of studies devoted to the practical development of syntheses on the basis of carbonyl compounds, until recently the existing ideas about the mechanisms of these processes were fairly vague. Systematic studies of the influence of the nature of the solvent and the size and charge of the cation on the kinetics and mechanisms of reactions with participation of carbonyl compounds began only in the last decade. Thus, the first model of the mechanism of the reactions of carbonyl compounds with organic derivatives of alkali metals, which is based on the extremely fruitful idea that the carbonyl group can be activated by the coordination of the oxygen atom to a metal cation and that the effective nucleophile (the group R of the organometallic compound) can be deactivated via association with formation of ion pairs, was constructed[1] in 1978. At the same time one must note that this, in essence, kinetic scheme clearly underestimates the thermodynamic factor known from other investigations, in particular, the fact that in the case of a thermodynamically sufficiently stable carbanion the addition to the carbonyl group can be reversible and the thermodynamic stability of the product should also depend on the cation and the solvent. Therefore, precisely at this time, when there has been a growth of interest in problems of the mechanism of the reactions of carbonyl compounds, it is necessary to perform a more detailed analysis of all the factors active in these processes in order to be able to base the formulation of the problems tackled in the later studies on the entire set of theoretical ideas in this field.

This review considers in the first place the reactions of organic derivatives of alkali metals with aldehydes and ketones, which lead to the formation of a C–C bond and for which data are available concerning the influence of the cation and the solvent on the rate and on the yield and composition of the products formed. Precisely for these reactions it is most often possible to relate the thermodynamic and kinetic parameters to the state of the organometallic compounds in solution (the type of ion pairs, the presence of free carbanions, the formation of associated species made up of ion pairs) and the ability of the cations to be coordinated to the carbonyl oxygen, which is of decisive importance for the determination of the process mechanism. An attempt has been made to consider critically the data in the original communications and to interpret them whenever possible from a single standpoint.

It is noteworthy that, from the standpoint of the effects of the medium on the cation, the reactions of organic derivatives of alkali (and alkaline earth) metals with carbonyl compounds and processes involving the reduction of the carbonyl group by alkali metal tetrahydroaluminates and tetrahydroborates have a great deal in common. Frequently the same workers have carried out parallel studies on processes of both types. For this reason, in certain cases, whenever this is necessary for the modelling of individual stages of the reaction or for the establishment of a more general picture, the review presents data on the reactivities of alkali metal enolates and cuprates and organomagnesium compounds and the hydride reduction reactions of the carbonyl group are also considered.

II. REACTIONS OF ORGANIC DERIVATIVES OF ALKALI METALS WITH ALDEHYDES

The reactions of organic derivatives of alkali metals and organomagnesium compounds with carbonyl compounds (aldehydes and ketones) can proceed in principle via three pathways:[2] addition, enolisation (when the carbonyl compound contains a sufficiently mobile proton), and reduction:



The relative contributions of each pathway are determined by the structure of the organometallic and carbonyl compounds, the charge and size of the metal ion M, the nature of the solvent, temperature, and certain other factors. It is simplest

to analyse the influence of the reaction conditions on the reaction rate and the final result in the interaction of organic derivatives of alkali metal compounds with aldehydes where only addition products are formed as a rule. However, we shall begin this Section with one of the most important features of the reaction involving addition to the carbonyl group—its reversibility.

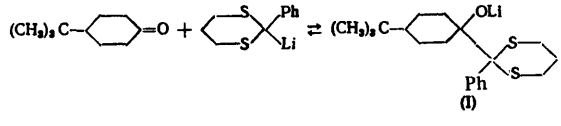
The idea of the reversibility of the nucleophilic addition to the carbonyl group probably arose in a study in 1950 of the kinetics of reactions in which organolithium compounds were chosen as nucleophiles.[3] The authors were able to explain the observed features only within the framework of a kinetic scheme including a rapid stage in which the alkoxide formed is cleaved into the initial reactants:

$$RM + \rangle C{=}O \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R{-}\underset{|}{\overset{|}{C}}{-}OM. \qquad (2)$$

Other investigators observed[4,5] that the ease of the analogous cleavage of alkoxides derived from β-hydroxyesters, namely $PhRC(OM)CH_2COOR'$ (where R = CH_3 and Ph and R' = C_2H_5, iso-C_3H_7, or t-C_4H_9), obtained by the metallation of the corresponding OH acids by alkali metal amides in toluene, liquid ammonia, and diethyl and dibutyl ethers, depends greatly on the size of the counterion. Thus the yield of benzophenone obtained when $Ph_2C(OM)CH_2COOC_2H_5$ was kept in liquid ammonia for several hours amounted to 89 and 71% for M = Na and K but was 0% when M = Li. The alkoxides $Ph_2CHC(OM)Ph_2$, where M = Na or K, are also cleaved fairly readily in ether and liquid ammonia with formation[6,7] of benzophenone and the alkali metal derivative of diphenylmethane.

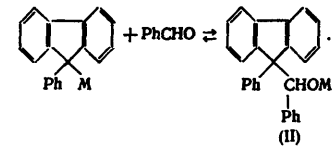
According to Cram's data,[8,9] the yield of the acetophenone formed on cleavage of alkoxides having the general formula $(C_2H_5)(CH_3)(Ph)C{-}C(CH_3)(Ph)(OM)$ in dimethyl sulphoxide (DMSO) increases sharply with increase in the radius of the alkali metal cation M: 25% for Li (24 h, 170 °C), 28% for Na (24 h, 75 °C), and 68% for K (12 h, 25 °C). The cleavage of alkali metal derivatives of trialkylcarbinols into the corresponding carbonyl compound and the organic derivative of the alkali metal takes place more effectively the greater the radius of the metal atom: Li < Na < K.[10]

The thermodynamic stability of the alkali metal alkoxide depends not only on the size of the alkali metal cation but also on the solvent. This is indicated by the clear decrease of the yield of the adduct (I) obtained by the addition of 2-lithio-2-phenyl-1,3-dithiane to 4-t-butylcyclohexanone: 90% in cyclohexane, 75% in tetrahydrofuran (THF), and 0% in hexamethylphosphoramide (HMP)† and also by the quantitative decomposition of this compound (obtained beforehand in cyclohexane) into the initial reactants when the solvent is replaced by HMP:



(I) (3)

Studies on the reactions of alkali metal derivatives of 9-phenylfluorene with benzaldehyde have shown[12,13] that the relative thermodynamic stability of the adduct, phenyl(9-phenyl-9-fluorenyl)alkoxide (II), diminishes simultaneously with increase of the radius of the metal atom and with increase of the polarity of the medium:



(II) (4)

In dimethoxyethane (DME), the yield of compound (II) diminishes in the sequence Li ≅ Na > K > Cs and on passing from solvents of the ethereal type to dipolar aprotic solvents. In HMP the decomposition of compound (II) into the initial reactants takes place regardless of the size of the metal atom. HMP destabilises not only compounds (I) and (II) but also the lithium and caesium alkoxides formed[14,15] in reaction (5) of alkali metal salts of diphenylacetonitrile, 1,3-diphenylindene, 9-methoxycarbonylfluorene, and fluoradene with benzaldehyde. In DME in the presence of 3–4 mole % HMP, the yield of RPhCHOM does not exceed 5%:[15]

$$PhCHO + RM \overset{K}{\rightleftarrows} RPhCHOM. \qquad (5)$$

As a result of the possibility of the spectroscopic measurement of the concentration of the alkali metal salt of the CH acid at any stage of its reaction with benzaldehyde, in particular when the reaction system attains the equilibrium position, measurements were made for the first time[14–16] of the equilibrium constant K and a study was made of the factors influencing this quantity. In the reaction of alkali metal salts of 9-phenylfluorene with benzaldehyde in DME, the equilibrium constant decreases monotonically with increase of the HMP concentration. For the lithium salt, K = 208, 25, and 6 litre mol^{-1} at HMP concentrations of 5.6, 8.2 and 10.7 vol.% and for the sodium salt the constant is 39.6, and 0.7 litre mol^{-1} at HMP concentrations of 1.4, 3.5, and 10.7 vol.%. In conformity with the results of qualitative observations,[4–10] K(Li) > K(Na) in the reaction medium of the same composition (10.7 vol.% HMP), which is associated with the greater thermodynamic stability of the lithium alkoxides.

Table 1. The equilibrium constants for the reactions[14–16] of alkali metal salts with benzaldehyde in DME at 25 °C.

CH acid (RH)	pK_a[a]	K, litre mol^{-1} ($c = 10^{-4}$ M)		
		Li^+	K^+	Cs^+
9-Benzylfluorene	22.0	—	—	>100
1-Methyl-3-phenylindene	—	—	—	38
Ethyl diphenylacetate	22.4	—	—	29
Diphenylacetonitrile	17.8	23	15	22
9-Phenylfluorene	18.5	—	14	15
1,3-Diphenylindene	12.8	16	—	2.4
Fluoradene	10.5	7.2	2.8	2.2
9-Methoxycarbonylfluorene	10.4	1.8	—	0.25
9-Cyanofluorene	8.5	—	—	0.32

[a]The pK_a were taken from Petrov et al.[17]

Measurements of the equilibrium constant have also been performed[14–16] in DME for the reactions of benzaldehyde with alkali metal salts of CH acids of different structure, whose pK_a were varied within the range of approximately 14 units (Table 1). The common features in the variation of the equilibrium constant are then as follows: (1) the increase of K with decrease of the thermodynamic stability of the reacting carbanion (in the presence of a fixed

†The main reaction pathway in HMP is enolisation, which will be examined in detail in the next Section of the review.

cation) whose measure is the pK_a of the conjugate CH acid and (2) the decrease of K with increase of the radius of the alkali metal cation (for a fixed CH acid). The variation of K in the sequence Li > K > Cs agrees with the results of the study of the thermodynamic stability of alkali metal alkoxides of different structure.[4-10] At the same time, the shift of equilibrium (5) towards the initial reactants with increase of the thermodynamic stability of the carbanion is a fact which is difficult to justify without rigorous quantitative measurements, although intuitively it appears to be fairly natural.

On the basis of the results of studies of equilibrium (5), an energetic approach has been developed[13,15] to the determination of the relative thermodynamic stability of the adducts. In this approach, account is taken of the fact that the alkali metal salts of CH and OH acids are ionic compounds and that they exist in solution in the form of an equilibrium mixture of free carbanions, ion pairs, and even (in the case of alkali metal alkoxides) associated species made up of ion pairs. One of the main factors influencing the position of equilibrium (5) is the energy of the interaction of the charged fragments of the ion pair $RPhCHO^-M^+$: the smaller this energy, the lower the value of K. The interaction energy diminishes with increase of the radius of the cation and of the degree of its solvation (in the presence of HMP and crown polyethers[13])—the equilibrium constant diminishes correspondingly. It is of interest that calculation for the gas phase[18] demonstrates a clear decrease of the C–H bond energy in alkali metal methoxides $H-CH_2OM$ on passing from Na (333 kJ mol^{-1}) to K (326 kJ mol^{-1}); the energy of the C–H bond is even lower in the free methoxide anion (306 kJ mol^{-1}). Presumably the interaction in the ion pair $-O^-M^+$ influences analogously the C–R bond energy in the alkali metal alkoxides $>C(OM)-R$.

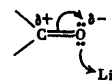
The study of the kinetics of the reactions of alkali metal salts of CH acids with benzaldehyde in DME established[14-16] that both free carbanions (rate constant k_i) and ion pairs (rate constant k_{ip}) participate in the stage involving addition to the carbonyl group:

$$\begin{array}{l} R^-M^+ \\ \downarrow\uparrow \\ R^- + M^+ \end{array} + PhCHO \underset{k_i}{\overset{k_{ip}}{\rightleftarrows}} RPhCHO^-M^+. \qquad (6)$$

Since two types of ionic species participate in the reaction and the reactivity of the free carbanions is appreciably higher than that of the ion pairs, the observed reaction rate constant k_1 depends on the concentration of the alkali metal salts of the CH acid in a fairly complex manner. At the same time the reverse reaction (k_{-1}) takes place only with participation of complex ion pairs $RPhCHO^-M^+$ and the observed rate constant is independent of the concentrations of the reactants.

The features characterising the changes in the rate constants k_i and k_{ip} (Table 2) as a function of the radius of the alkali metal cation and the structure of the carbanion resemble those observed in nucleophilic aliphatic substitution reactions[19] with participation of alkali metal salts of CH acids. However, there are also significant differences. A common feature is the higher reactivity of free carbanions regardless of the variation of other factors, i.e. $k_i > k_{ip}$. Since in virtually all cases (with the exception of the lithio-derivatives of 1,3-diphenylindene and fluoradene)[15,20] the ion pairs of the alkali metal salts investigated are of the contact type, k_i exceeds k_{ip} approximately by two orders of magnitude. In a reaction system with solvate-separated ion pairs (1,3-diphenylindenyl-lithium), k_i/k_{ip} is appreciably lower (~13).

A new factor, which was not encountered previously in the reactions of alkali metal salts of CH acids, is the dependence of the rate constant for the reaction of the free carbanion on the radius of the alkali metal caton when lithium and caesium salts are compared. In the case of alkali metal derivatives of diphenylacetonitrile, 1,3-diphenylindene, and fluoradene, $k_i(Li^+)$ exceeds $k_i(Cs^+)$ by a factor of 6–15, while for the reactions of alkali metal salts of 9-methoxycarbonylfluorene the difference between $k_i(Li^+)$ and $k_i(Cs^+)$ approaches two orders of magnitude. In order to account for this result,[14,15] one can invoke the idea, put forward by Lefour and Loupy,[1] that the carbonyl group is activated by the formation of a complex between the Li^+ cation and the oxygen atom:



Complex formation entails an increase in the electrophilicity of the carbonyl group, because there is an increase[1,21] in the positive charge on the carbon atom and a decrease of the LUMO energy. According to calculated data in two communications,[1,21] the formation of complexes between Li^+ and acroleine, benzaldehyde, acetophenone, and aliphatic aldehydes in the gas phase results in a decrease of the LUMO energy in these carbonyl compounds by 600–700 kJ mol^{-1}. Since there are experimental facts[21] indicating the possibility of controlling the reactions of carbonyl compounds and organic derivatives of alkali metals by means of the LUMO and HOMO energies, these calculations merit special attention. While coordination to Li^+ lowers[1] the energy of the LUMO of acroleine by 695 kJ mol^{-1}, coordination to Na^+ alters the LUMO energy by 454 kJ mol^{-1}. Large cations, for example Cs^+, have little influence on the LUMO energy of the carbonyl compound. Such is the theoretical assessment of the possibilities of the coordination of the cation to the carbonyl group.

Table 2. The rate constants[a] for the reactions involving the addition[15,16] of the free carbanions (k_i) and their ion pairs (k_{ip}) to the carbonyl group of benzaldehyde in DME at 25 °C.

CH acid	M^+	$10^3 k_i$	$10^5 k_{ip}$
9-Methylfluorene	Cs^+	310	840
Diphenyl(2-pyridyl)methane	Cs^+	170	570
Diphenylacetonitrile	Li^+	203	224
"	Cs^+	13.5	24.7
1,3-Diphenylindene	Li^+	8.8	66
"	Cs^+	0.85	0.34
Fluoradene	Li^+	4.66	—
"	Cs^+	0.83	1.33
9-Methoxycarbonylfluorene	Li^+	22.8	2.26
"	Cs^+	0.32	0.52
9-Cyanofluorene	Cs^+	0.14	0.24

[a]The dimensions of the constants are litre mol^{-1} s^{-1}.

Experimental data have confirmed[22-25] the possibility of the formation of complexes of Li^+ with aldehydes and ketones. However, these data have been obtained in studies in solutions in the carbonyl compounds themselves,[22] in acetonitrile,[23,24] and in aqueous alcoholic mixtures.[25] On the other hand, when one is dealing with the coordination of an alkali metal cation to the carbonyl group in solvents of the ethereal

type, many questions arise. Firstly, there are no convincing thermodynamic data in support of such coordination. It is known that the basicity of ethereal solvents is as a rule higher than the basicity of carbonyl compounds. For example, the Kamlet–Taft basicity parameters B_{CT} [26] for acetone and cyclohexanone are respectively 0.37 and 0.41, while the values for ether and THF are respectively 0.49 and 0.47. The change in ΔH on formation of a complex between Li^+ and THF, DME, and glymes by 0.3–20 kJ mol^{-1} in absolute magnitude exceeds the corresponding parameter for the reaction of Li^+ with acetone.[27] Admittedly there are data[28] showing that the energies of the complex formation reactions of Li^+ with ether, formaldehyde, and acetaldehyde are similar: −163, −149, and −169 kJ mol^{-1} respectively.

Secondly, in the reaction medium the concentration of the carbonyl compound is usually lower by one–two orders of magnitude than the concentration of the ethereal solvent. Thus, even if the complex of the alkali metal cation with the carbonyl group is formed, its concentration should probably be small and should depend greatly on the reaction conditions.

At the present time the concept[1] of the formation of a complex of the alkali metal cation with the carbonyl group is widely used[21,29–35] also in the interpretation of the results of studies on reactions of lithio-derivatives with aldehydes and ketones. One can therefore mention also data obtained in the investigation of related systems. The fluoradenyl anion[36] and carbanions of the benzyl type[37] react with epoxyethane more slowly than their lithium ion pair because, according to the authors' hypothesis, the cation forming part of the composition of the ion pair cooperates with the opening of the epoxide ring by being coordinated to the oxygen atom.

Among the results obtained[16] in the study of the kinetics of the reactions of alkali metal salts of CH acids with benzaldehyde, yet another experimental fact is of great interest. The rate constants for the addition of the carbanions (k_i) and their caesium ion pairs (k_{ip}) to the carbonyl group vary in parallel with the rate constants for the reactions of the same species in nucleophilic aliphatic substitution processes. Furthermore, the logarithms of the nucleophilic addition and nucleophilic substitution rate constants are linearly related. This shows that the nucleophilic properties of the ionic species determine their reactivity in both processes.

Interesting effects of the medium and the cation have been observed[29] in the reactions of alkali metal derivatives of nitriles with benzaldehyde and its *para*-substituted derivatives. The yield of the adducts (III) in reaction (7) does not depend greatly on the size of the metal atom—98% for Li, 70% for Na, and 80% for K, but it nevertheless reaches its maximum value in the reaction with the lithium salt:

$$MCH_2CN + PhCHO \rightarrow \underset{(III)}{PhCH(CH_2CN)OM}. \qquad (7)$$

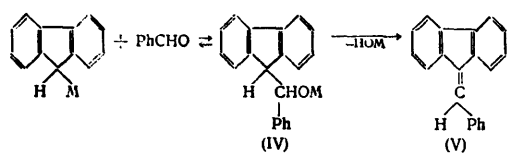
In the light of the foregoing examination of the interactions of alkali metal salts of CH acids with aldehydes, these data constitute indirect evidence for the reversibility of reaction (7), although the authors[29] make no mention of this important factor. Incidentally, if the equilibrium constants of reaction (7) are estimated by assuming that the initial reactant concentrations are 0.1 M,[29] then entirely reasonable values are obtained: 10^4 for Li, 80 for Na, and 200 litre mol^{-1} for K. Taking into account the fact that reaction (7) was carried out in THF and not in DME and at −80 °C and not at 25 °C (pK_a for acetonitrile is 24), the constants obtained agree fairly well with the data presented in Table 1. It is of interest that the variation of the equilibrium constant as a function of the cation ($Li^+ > K^+ > Na^+$) is of the same character both for the reactions of alkali metal salts of diphenylacetonitrile[15] and for the reactions of alkali metal salts of acetonitrile. Judging from the time required to complete reaction (7), its rate varies in the sequence Li > Na > K. This result (subject to the condition that both free carbanions and ion pairs or even associated species comprising ion pairs react in THF at an alkali metal salt concentration of 0.1 M) clearly indicate the involvement of the cation in the activation of the carbonyl group. This is confirmed by the decrease of the rate of reacton following the addition of cryptand 211 to the lithium salt of acetonitrile. However, the rate of reaction of KCH_2CN in the presence of cryptand 222 increases, which the authors[29] believe is also associated with the increase of the fraction of free carbanions. On the other hand, cryptand 221 does not influence the rate of reaction of $NaCH_2CN$, which the authors explained by the cancellation of two effects—on the one hand, the suppression of the activation of the carbonyl group and, on the other, the increase of the contribution of the reaction involving the more reactive free carbanions.

The half-life of the reaction of the lithium salt of *m*-chlorophenylacetonitrile with aromatic aldehydes in THF at −80 °C diminishes in the following sequence of X: CN (15 min) > H (10 min) > OCH_3 (5 min). When HMP is added, the sequence is reversed: CN (0.5 min) < H (2 min) < OCH_3 (45 min):

$$m\text{-}ClC_6H_4CH(CN)Li + p\text{-}XC_6H_4CHO \rightarrow m\text{-}ClC_6H_4\underset{\displaystyle p\text{-}XC_6H_4CHOLi}{\underset{|}{CH}}(CN). \qquad (8)$$

The rate of reaction of anisaldehyde diminishes, while other aldehydes react faster. The authors have interpreted these results[29] from the standpoint of the positions of the energy levels of the LUMO of the aldehyde relative to the HOMO of the carbanion assuming that, by virtue of the coordination of Li^+ to the carbonyl group, in THF the energies of the LUMO of all three aldehydes are equalised and are lower than the energies of the corresponding LUMO in a THF–HMP mixture, where such coordination does not occur.

The study of the reactions of alkali metal salts of fluorene with benzaldehyde under different conditions yielded[12,13] data concerning the influence of the solvent and the cation not only on the stage involving the addition of the nucleophile to the carbonyl group but also on the next stage in which a molecule of the alkali is eliminated, i.e. on the process modelling the crotonic condensation. In contrast to their 9-substituted derivatives, the unsubstituted fluorenyl salts [cf. Eqn. (4)] react with benzaldehyde in accordance with the following scheme:



(9)

The conversion of fluorenyl-lithium or fluoroenylsodium into the reaction products in ether and DME at concentrations of organic derivatives of alkali metals in the range 0.01–0.1 M and those of benzaldehyde in the range 0.03–0.4 M takes place over a period shorter than 1 s. The lithium and sodium salts of fluorene in HMP or its potassium, caesium and tetra-n-butylammonium salts in any of the solvents employed (ether, DME, HMP) react appreciably more slowly. Under these conditions, the complete consumption of the carbanion requires about 1 min. The retardation of the reactions in ether and DME in the presence of K^+, Cs^+, and $Bu_4^nN^+$ compared with Li^+ and Na^+ or the retardation of the reactions of

fluorenyl-lithium and fluorenylsodium on passing to HMP (or after the introduction of solvating additives of the type of crown polyethers) is due to the appreciable shift of the equilibrium in the first stage of reaction (9) towards the initial reactants. In HMP or in the presence of large cations in ether and DME, the reactions considered in essence occur generally only because of the irreversible alkali elimination stage. For this reason, the only observed reaction product under these conditions is benzylidenefluorene (V).

In other cases the composition of the products depends on the competition between the first and second stages. A common feature is the increase in the yield of benzylidenefluorene with increase of the basicity (or with decrease of the thermodynamic stability) of the alkali metal alkoxide formed. The yield of benzylidenefluorine increases with increase of the polarity of the medium in the presence of the given cation (benzene < ether < DME < HMP in the presence of Li^+ and Na^+) and with increase of the radius of the cation in the given solvent. In DME: Li^+ (9%) < Na^+ (77%) < K^+, Cs^+, Bu_4N^+ (100%); in ether: Li^+ (16%) < Na^+ (70%) ≅ K^+ (69%); in benzene: Li^+ (0%) < Na^+ (23%) < Cs^+ (42%).

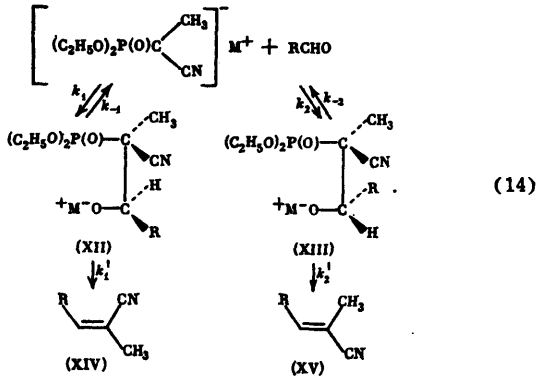
Whereas the elimination stage is irreversible in the reactions of alkali metal salts of fluorene and benzaldehyde, both stages are reversible in the Knoevenagel condensation [reaction (10)], where X and Y = CN or COOR:

$$XYCHM + PhCHO \rightleftarrows XYCHCHOM \underset{+HOM}{\overset{-HOM}{\rightleftharpoons}} XYC{=}CHPh. \qquad (10)$$
$$\quad\quad\quad

oxygen atoms and they are thus both arranged in the transition state in such a way that the electrostatic repulsion between them is minimal:[43]



The conditions of the Horner–Emmons reaction also have an appreciable influence on the composition of the products formed (Table 3):[44,45]



(14)

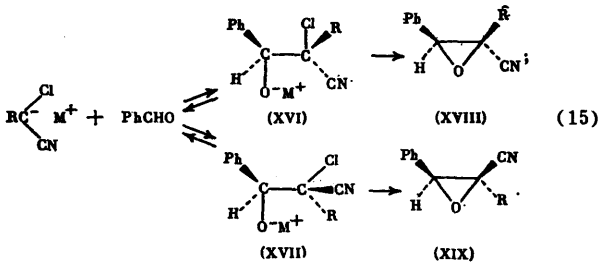
Table 3. The composition of the products of reaction (14) in THF as a function of temperature and the size of the alkali metal cation.[44,45]

R	t, °C	Li+ (XIV)[a]/(XV)	Li+ (XIV)[b]/(XV)	Li+ k_{-1}/k_1'	Na+ (XIV)[a]/(XV)	Na+ (XIV)[b]/(XV)	Na+ (XIV)[c]/(XV)	K+ (XIV)[a]/(XV)	K+ (XIV)[b]/(XV)	K+ k_{-1}/k_1'
Ph	−78	0.43	3.0	0.6	1.0	—	—	9.0	19	1
	20	0.33	0.43	13	0.66[d]	4[e]	0.03[f]	1.5	—	—
	65	0.25	0.33	15	0.54	—	—	1.0	1.5	4
p-$CH_3OC_6H_4$	−78	0.25	1.5	1	0.43	—	—	2.33	9.0	0.5
	20	0.25	—	—	0.43	—	—	1.5	—	—
	65	0.33	0.33	>40	0.64	—	—	1.02	1.02	>40

Remarks. Procedure followed in carrying out the reactions: [a]by mixing the initial reactants; [b]by starting with compound (XII): [c]by starting with compound (XIII); the ratios (XIV)/(XV) in HMP are [d]0.25, [e]16, and [f]0.02.

The aldol condensation stage in reaction (14) is reversible. For this reason, the product (XV) is formed, as shown by the authors,[44,45] not only on mixing the initial reactants but also when compound (XII), obtained by an independent procedure, is maintained in solution in THF or HMP (Table 3). Similarly, compound (XIV) can be obtained when compound (XIII) is kept in HMP or THF. The possibility of carrying out the experiment with compound (XII) or (XIII) obtained beforehand determines to a large extent the ratio of compounds (XIV) and (XV) formed ultimately. At low temperatures the decomposition of the alkoxides (XII) and (XIII) into the initial reactants (k_{-1}, k_{-2}) is relatively slow and this is why compounds (XIV) and (XV) are formed preferentially from compounds (XII) and (XIII) respectively. At high temperatures, the equilibration process is rapid (k_{-1}/k_1' and k_{-2}/k_2' are large), so that the product ratio (XIV)/(XV) is almost independent of the way in which the experiment is carried out (Table 3).

The epoxynitriles (XVIII) and (XIX) are formed in reaction (15) also via the reversible stage involving nucleophilic addition to the carbonyl group:[46]

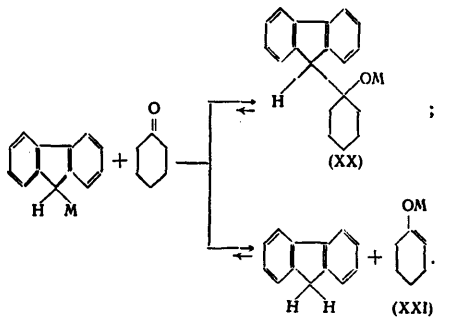


(15)

When a 1:1 mixture of compounds (XVII) and (XVI) synthesised beforehand is kept in HMP (Na^+), benzene (Na^+ and Li^+), and THF (K^+ and Li^+), the ratio of the products formed (XIX)/(XVIII) is respectively >98, 0.43, 4.4, and 9. If PhCHO and RC(CN)(Cl)M are mixed, then compound (XIX) predominates among the products of reaction (15): the ratio (XIX)/(XVIII) exceeds 98 for Li^+ in THF and benzene, while for Na^+ in HMP and THF and for K^+ in THF the ratio (XIX)/(XVIII) is respectively >98, 4, and 4. The only exception is the reaction of the sodium salt in benzene for which (XIX)/(XVII) is 0.18.

III. REACTIONS OF ORGANIC DERIVATIVES OF ALKALI METALS WITH KETONES

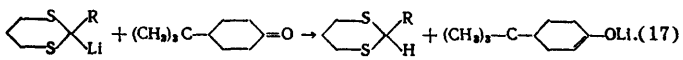
The reactions of organic derivatives of alkali and alkaline earth metals with ketones having a fairly mobile proton can lead to the formation[2] of both an adduct and an enolisation product. In this case detailed studies of the effects of the medium and the cation have been performed[12,47,48] in relation to the reactions of alkali metal salts of fluorene with cyclohexanone via the mechanism



(16)

In all the solvents investigated, the yield of the adduct (XX) increases with decrease of the radius of the cation. In DME: Bu_4N^+, Cs^+, K^+ (0%) < Na^+ (5%) < Li^+ (13%); in ether: Cs^+ (0%) < Na^+ (27%) < Li^+ (72%); in benzene: Cs^+ (7%) < Na^+ (33%) < Li^+ (80%). On the other hand, the yield of compound (XX) in the reactions of all the alkali metal salts investigated increases on passing to non-polar non-solvating media. HMP (0%) < DME (15%) < ether (72%) < benzene (80%) for Li^+, DME (5%) < ether (27%) < benzene (33%) for Na^+, and HMP, DME (0%) ≅ ether (0%) < benzene (7%) for Cs^+. In HME the equilibrium is fully displaced towards the initial

reactants. On the other hand, in the reaction of 2-lithio-1,3-dithiane and 2-lithio-2-phenyl-1,3-dithiane with 4-*t*-butylcyclohexanone, HMP has a somewhat different influence. In this solvent, the adduct (I) is not formed[11] and enolisation takes place instead:



(17)

Thus the enolate is not formed in the reaction of fluorenyllithium with cyclohexanone in HMP,[47,48] but enolisation does occur in reaction (17) in the same solvent. This apparent contradiction can be readily accounted for if one turns to the results obtained[49] in a study of the basicity of alkali metal enolates of cyclohexanone (and also cyclopentanone, ethyl methyl ketone, and acetophenone). In the presence of cryptands, the lithium, sodium, and potassium enolates of cyclohexanone ($pK_a = 18$) [50] metallate quantitatively triphenylmethane ($pK_a = 31.5$) [51] and diphenylmethane ($pK_a = 33$) [51] in THF, which is itself surprising merely on the basis of a comparison of the above pK_a for these compounds. The sharp increase of the basicity of the alkali metal enolates of cyclohexanone is caused by the fact that, in the presence of cryptands, they probably exist in the form of solvate-separated ion pairs (or even partly in the form of free enolate ions).

Thus it has been found that HMP, whose action is analogous to that of cryptands, increases the basicity of alkali metal enolates of cyclohexanone so much that they metallate quantitatively fluorene ($pK_a = 23$), fully displacing to the left the transprotonation equilibrium in scheme (16) (as well as the addition equilibrium). On the other hand, the pK_a for 1,3-dithianes are probably sufficiently high for enolisation in accordance with scheme (17). It is significant that enolisation does not occur in the reactions of alkali metal salts of fluorene with cyclohexanone also in DME[47,48] when the cations are K^+, Cs^+, or $(C_4H_9)_4N^+$. This shows that the basicity of the enolates increases also with increase of the radius of the cation.

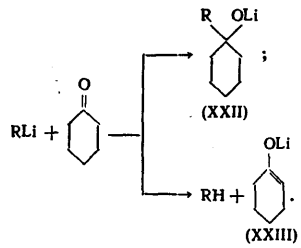
The yield of the adduct in the reactions of alkali metal salts of fluorene with cyclohexanone depends on the presence[47,48] of added inorganic lithium salts in the reaction system. Thus the yield of compound (XX) in the reaction of fluorenyllithium increases from 13 to 30% as a result of the introduction of $LiClO_4$ into DME. The yield of the product of the addition of propynyl-lithium to cyclohexanone or cyclopentanone increases analogously[52] to 80–90% under the influence of LiBr (in the absence of the salt, the yield varies in the range 40 to 60%).

LiBr exerts an unusual influence on the reaction of fluorenylpotassium and fluorenylcaesium with cyclohexanone in DME. The addition of this salt leads[48] to the instantaneous consumption of the carbanion but only the alkali metal enolate is formed in this process. The observed effect is probably determined in the first place by the occurrence of the exchange reaction[53,54]

$$RM + LiX \rightleftarrows RLi + MX. \qquad (18)$$

However, the absence of an adduct[48] suggests that LiBr activates not only the carbonyl group but also the α-CH bond of the ketone. On the other hand, the activated ketone enters preferentially into the enolisation reaction in this instance. This result agrees in general with the observed behaviour in the reactions of alkali metal salts of fluorene with cyclohexanone in DME: the yield of alkoxides in these reactions is always lower than that of the enolates.[47,48]

The interaction of alkyl organolithium compounds with cyclohexanone in ether or DME takes place[30,31] in accordance with scheme (19) which is analogous to scheme (16):



(19)

However, by virtue of the low CH acidity of RH ($pK_a > 40$) [55] and the high basicity of RLi, in this case both reaction pathways are apparently almost irreversible. The composition of the product is in this instance strongly influenced[30,31] by ionic and solvating additives. When cyclohexanone interacts with n-butyl-lithium, t-butyl-lithium, and ethynyl-lithium, the adducts (XXII) are formed rapidly in the first two instances and slowly in the last with a quantitative# yield.[30,31] In the presence of cryptand 211 in these reaction systems, enolisation takes place exclusively but, if apart from the cryptand, an equimolecular amount of LiBr is also introduced into the mixture, then compound (XXII) again becomes the only reaction product. In order to explain the results the authors used the concept of the activation of the carbonyl group by the formation of its complex with Li^+. The cryptand, which effectively binds Li^+, does not allow the cation to be coordinated to oxygen and LiBr plays the role of a donor of Li^+ ions capable of coordination.

A strong influence of the cryptand has been observed[30] also in a study of the reactions of n-butyl-lithium with the ethyl esters of benzoic, αα-dimethylpropionic, and α-methylpropionic acids. In ethereal solvents the alkyl-lithium compound adds to the carbonyl group while the addition of cryptand 211 fully inhibits the reaction and the initial esters can be isolated quantitatively from the reaction medium. Furthermore, it has been found[30] that cryptand 211 influences analogously also the reactions of alkyl-lithium compounds with carboxylic acids. In the presence of a large excess of n-butyl-lithium, it adds to the carbonyl group of benzoic, αα-dimethylpropionic, and α-methylpropionic acids (more precisely their lithium salts, which should be formed in the first stage). On the other hand, the cryptand precludes this addition owing to the absence, according to the authors,[30] of the coordination of Li^+ to the carbonyl oxygen atom.

The yield of the adduct can be increased[2] and that of the enolate decreased by lowering the reaction temperature. Whereas the addition of n-butyl-lithium to acetone, cyclohexanone, cyclopentanone, norcamphor, and acetophenone in ether at 0 °C proceeds respectively to the extent of 67, 82, 63, 76, and 73%, at −78 °C the respective yields are 80, 89, 75, 81, and 81%. Furthermore, it has been found that, in the reaction of t-butyl-lithium with various ketones, the yield of the adduct is lower (amounting to 50–70% depending on the structure of the ketone) than in the reaction with n-butyl-lithium and in the case of cyclohexanone it amounts to 53% (and not 100% as indicated by the studies of Perraud

#According to Van Rijn et al.[52], the yield of the products of the addition of n-butyl-lithium to cyclohexanone usually does not exceed 80%.

and Handel[30,31]). The relative increase of the yield of the adduct with increasing temperature can probably be caused by two factors—the lower activation energy for the addition of the alkyl-lithium compound to the carbonyl group compared with the proton transfer reaction and/or the higher thermodynamic stability of the alkoxide compared with the enolate. It is noteworthy that the fraction of the adduct increases[47] with increase of temperature also in the reaction of fluorenyllithium with cyclohexanone in DME.

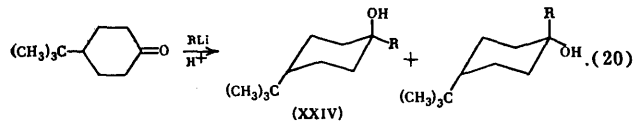
Analogously to the observations made[47,48] in the reactions of alkali metal salts of fluorene, an increase in the size of the cation lowers[2] the effectiveness of the addition reaction: t-butyl-lithium makes it possible to obtain 53% of 1-t-butyl-1-cyclohexanol, while t-butylsodium produces only 7% of this compound. According to O'Sullivan et al.[56], the yield of the adduct increases not only with decrease of the radius of the alkali metal cation but also on passing from organolithium, organosodium, and organopotassium derivatives to organomagnesium derivatives. In the reactions of a series of PhM with acetophenone, the ratio of the yield of the adduct to that of the enolisation product is 1:10 (hexane) for M = K, 1:1.4 (heptane) for M = Na, and 23:1 (ether) for M = Li. Enolisation does not occur at all when M = MgCl.[56]

In the synthesis of graft copolymers [in the reactions of polystyryl-lithium and polystyrylpotassium with poly(methyl methacrylate) and the copolymers of styrene with methyl vinyl ketone, acroleine, or methyl methacrylate], the degree of grafting (i.e. the fraction of the adduct) is always higher[57] when the reaction is carried out in non-polar media and not in THF and when the carbanion with the lithium counterion enters into the reaction with the carbonyl functional group. In the reaction of a carbanion of the benzyl type (the polystyryl anion) with 3-methyl-2-pentanone,[57] the yield of the adduct increases with decrease of the radius of the alkali metal cation (i.e. with increase of its affinity for oxygen) and on passing from THF to cyclohexane. Thus K^+ (20%) < Na^+ (50%) < Li^+ (73%) in THF and K^+ (48%) < Na^+ (59%) < Li^+ (79%) in cyclohexane. In this case too, the authors[57] believe that the addition is promoted by the coordination of Li^+ to the carbonyl group.

The addition of dimethylmagnesium to benzophenone has been investigated[58] in ether in the presence of various solvating additives. The authors established that dimethylmagnesium enters into the reaction in the form of 1:1 and 1:2 complexes with bidentate and monodentate solvating compounds respectively, the addition taking place without the elimination of ligands. Depending on the nature of the ligand, the reaction is accelerated (dimethyl ether, triethylamine, DME, HMP, β-methoxyethyldimethylamine) or retarded (THF, dioxan, tetramethylethylenediamine).

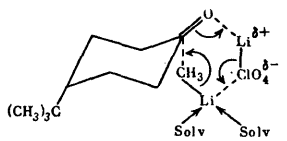
In the reactions of organomagnesium compounds with ketones, the composition of the products can be appreciably altered[59] by changing the nature of the medium, as happens in the case of organic derivatives of alkali metals. In the reaction of n-propylmagnesium bromide with diisopropyl ketone in ether, the ratio of the adduct and the reduction product is 37:63, increasing appreciably in benzene (to 64:36). An analogous situation has been observed in the reaction of n-propylmagnesium bromide with cyclohexyl isopropyl ketone (48:52 in ether and 86:14 in benzene) and with isopropyl propyl ketone (5:35 in ether and 13:61 in benzene). In the reaction with isopropyl propyl ketone, an appreciable amount of the enolisation product is also formed, its yield falling on passing from ether (60%) to benzene (26%).

By varying the conditions in the reactions of organolithium compounds with 4-t-butylcyclohexanone [reaction (20)], it has been possible to alter,[60-62] albeit not within very wide limits, the ratio of the axial isomers (XXIV) and the equatorial isomers of the alcohols formed:



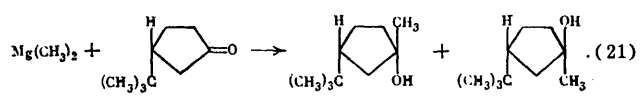
(20)

In the reaction of methyl-lithium[61] in THF at −78 °C, the fraction of compound (XXIV) is 65–69%. The introduction of LiBr, LiI, $LiClO_4$, or $LiCu(CH_3)_2$ into the solution does not influence the yield of compound (XXIV). When the reaction is carried out in ether at −78 °C, the above additives make it possible to increase the fraction of compound (XXIV) to 87–92%.[61] The addition of $LiClO_4$ also increases somewhat[62] the yield of compound (XXIV) (from 58 to 69%) in the reaction of phenyl-lithium carried out under the same conditions. On the other hand, the increase of temperature from −78° to +5 °C lowers[60] the fraction of compound (XXIV)—for example, in the reaction of 4-t-butylcyclohexanone with n-butyl-lithium and s-butyl-lithium. The authors[60,61] believe that the influence of added inorganic lithium salts on temperature is manifested only when the reaction is performed in ether, because its complex forming effect does not greatly exceed the ability of the ketone to form a complex with Li^+. For this reason, in the reactions of a wide range of cyclic ketones with methyl-lithium in ether, the addition of lithium perchlorate should promote[62] the formation of a transition state from which only the axial isomer can be obtained.



It is noteworthy that it is very difficult to treat systematically the influence of the solvent on the stereoselectivity of the reactions of organolithium compounds with cyclic ketones, because each reaction system as a rule reacts in a fairly individual manner. In the reaction of ethynyl-lithium with 2-methylcyclohexanone,[63] the fraction of the axial alcohol is appreciably higher when the reaction is carried out in a non-polar solvent (benzene, 67%) than in THF (42%). The axial isomer is formed analogously in the reaction of ethylnylsodium[63] with a higher yield in benzene (53%) than in the polar THF–NH_3 mixture (41%). On the other hand, both in ether and in THF the product (XXIV) is formed[60] in virtually the same yield—69 and 65% respectively. In the reaction with 7-norbornene, n-butyl-lithium affords[64] 50% of the *endo*-isomer both in ether and in n-hexane. This is also true of the reaction of phenyl-lithium;[64] the yield of the *endo*-isomer is 72% in both solvents.

The solvent has an even weaker influence on the stereoselectivity of the reactions of organomagnesium compounds. In the reaction of dimethylmagnesium with 3-t-butylcyclopentanone, i.e.



(21)

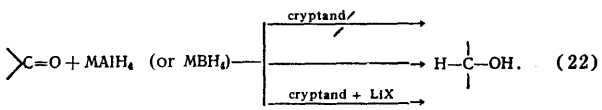
(XXV)

the yield of the *cis*-isomer (XXV) is the same[65] in ether (53%), THF (52%), and anisole (54%). The yield of compound (XXV) is independent of the solvent (THF, anisole, ether); when methylmagnesium bromide reacts[65] with 3-t-butylcyclopentanone, the yield is again 53–54%.

The change of the cation in the reactions of organic derivatives of alkali metals with cyclic ketones has as a rule only a weak influence on the stereoselectivity, especially as the process takes place in a solvent which effectively solvates the alkali metal cations. The reaction of ethynyl-lithium and ethynylpotassium with 3-methylcyclohexanone in the THF–NH_3 mixture leads mainly to the equatorial isomer:[63] 82% (Li^+) and 80% (K^+). In the same medium but in the reaction of 2-methylcyclohexanone with HC≡CM the yield of the equatorial isomer falls but a dependence on the cation cannot be observed:[63] 45% (Li^+), 41% (Na^+), and 44% (K^+). Only in benzene is the yield of the axial isomer somewhat higher[63] in the presence of Li^+ (67%) than in the presence of Na^+ (53%).

IV. THE HYDRIDE REDUCTION REACTIONS OF CARBONYL COMPOUNDS

Numerous studies[32–35,66–69] of the effects of the medium and the cation on the reduction of carbonyl compounds by alkali metal tetrahydroaluminates and tetrahydroborates have been published in recent years. The methodology of the majority of these investigations and their results are similar. They can be represented in the following form:

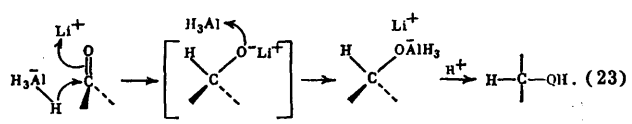


(22)

We shall examine initially the results obtained in the study of the reactions of alkali metal tetrahydroaluminates. In ethereal solvents (DME, THF, ether, diglyme), $MAlH_4$ (where M = Na or Li) reduces cyclohexanone,[32,33] 2-methylcyclohexanone,[66] 4-t-butylcyclohexanone,[66] cyclopentanone,[32] *N*-t-butylacetyl-2-aziridine,[35] α-chloropropiophenone,[67] benzaldehyde,[21] acetophenone,[21] p-methoxyacetophenone,[21] and compounds[32] having the general formula $C_2H_5C(O)X$, where X = H, OH, or C_2H_5, to the corresponding hydroxy-derivatives. In the present of cryptand 211 for M = Li and cryptand 221 for M = Na, hydroxycompounds are not formed[32,33,35,66,67] or, much more rarely,[21] the rate of their formation is sharply reduced. The rate of reduction is also lowered by the addition of crown ethers[68] and hexamethyltriethylenetetra-amine[34] but their effect is much weaker than that of cryptands.

Finally, if an inorganic lithium salt (LiBr, LiI, $LiClO_4$) [32, 33,35] or sodium salt ($NaClO_4$) [33,35] is introduced into the reaction medium in addition to the cryptand, the effect of the latter is fully removed and quantitative reduction of the carbonyl compound is observed.

In order to account for the results, the idea of the activation of the carbonyl group as a result of the formation of a complex of the latter with an alkali metal cation has been used, as for the reactions involving organometallic compounds discussed above. For example, the reaction involving reduction by lithium tetrahydroaluminate has been described in this way:[33]



(23)

The reaction does not occur in the presence of cryptands, because the possibility of the formation of a complex between the alkali metal cation and the carbonyl group is then eliminated. On the other hand, if the reaction is carried out in the presence of equimolar amounts of lithium tetrahydroaluminate, the cryptand, and an inorganic lithium salt, then one equivalent of Li^+ ions not involving the complex remains for the activation of the carbonyl group.

It is surprising that no attention has been paid in any of the studies quoted to what may occur in the reaction mixture in the presence of the cryptand. After all the latter not only eliminates the possibility of the formation of a complex between the cation and the carbonyl group but in its presence there should be an appreciable increase of both the nucleophilicity and the basicity of the negatively charged tetrahydroaluminate fragment, which has been demonstrated by investigations of the reactions of organolithium compounds.[30,31] It is extremely likely that in the presence of cryptands $MAlH_4$ nevertheless reacts with ketones but via the transprotonation and not the addition mechanism, i.e. by enolising suitable carbonyl compounds. This has been confirmed indirectly by the finding that cyclohexanone is converted into the enolate under the influence of sodium, potassium, and lithium hydrides when cryptands are present in the reaction medium.[69] Yet another interesting question arises: is it possible to account for the influence of cryptands by the reversibility of the addition of the hydride to the carbonyl group? Although there is no experimental evidence in support of this claim, nevertheless this hypothesis is entirely reasonable.

The behaviour observed for the reactions of tetrahydroaluminates, discussed above, holds in general also for the reactions of alkali metal tetrahydroborates. Cryptands suppress the reduction of *N*-t-butylacetyl-2-aziridine,[35] cyclohexanone[33] and α-chloropropiophenone.[67] However, when $LiClO_4$ [33] or $NaClO_4$ [33,35] is introduced into the system together with the cryptand, the effect of the latter is removed. In contrast to $MAlH_4$, the reactions of MBH_4 can be carried out in hydroxylated solvents (water, alcohols) where the carbonyl group can be activated by the formation of hydrogen bonds with solvent molecules.[35,66,67,70] In methanol, *N*-t-butylacetyl-2-aziridine [35] is reduced rapidly by $NaBH_4$ regardless of whether the cryptand 221, $NaClO_4$, or $LiClO_4$ are present in the reaction medium. The addition of water to an ethereal solvent makes it possible to obtain the product of the addition of *N*-t-butylacetyl-2-aziridine,[35] α-chloropropiophenone,[67] 2-methylcyclohexanone,[66] and 4-t-butylcyclohexanone[66] even if the solvent contains the cryptand.

Lithium tetrahydroborate reacts faster with carbonyl compounds than sodium tetrahydroborate, which has been observed in most varied solvents: pyridine,[71] isopropyl alcohol,[54,70] and water.[70] Thus $LiBH_4$ reduces ethyl benzoate in isopropyl alcohol, while $NaBH_4$ does not.[54] The rate constant for the reaction[70] of acetone with $LiBH_4$ in the same solvent (5×10^{-3} litre mol^{-1} s^{-1}) is almost three times as high as that for the reaction with $NaBH_4$ (1.5×10^{-3} litre mol^{-1} s^{-1}). However, in all cases this result is attributed to the more effective coordination of Li^+ (compared with Na^+) to the carbonyl group, which is sometimes believed[71] to be due to the higher nucleophilicity of the lithium ion pair (although without any special supporting evidence).

The importance of the activation of the carbonyl group is also indicated by data obtained in the study of the reduction of acetone[70] and esters[54] by tetrahydroborates. The reaction with $NaBH_4$ takes place only in water and alcohols and its rate increases with increase of the electron-donating capacity of the solvent: isopropyl alcohol < H_2O, ethanol. In acetonitrile, pyridine, DMF, and diglyme, $NaBH_4$ hardly reacts with acetone. Esters are not reduced by $NaBH_4$ [54] even in isopropyl alcohol. The addition of LiI and LiCl accelerates[70] the reduction of acetone by both $NaBH_4$ and

$LiBH_4$. In the presence of LiBr, ethyl acetate, ethyl stearate, ethyl benzoate, ethyl cinnamate, and ethyl *p*-chlorobenzoate begin to react with $NaBH_4$.[54] Here one must note that, whereas the acceleration of the reaction involving $LiBH_4$ can be accounted for solely by electrophilic catalysis, in the case of $NaBH_4$ inorganic lithium salts give rise to the possibility of cation exchange as well[54] [reaction (24)], so that subsequently the process can proceed with participation of $LiBH_4$:

$$NaBH_4 + LiX \rightleftarrows LiBH_4 + NaX. \qquad (24)$$

The reduction of esters by $NaBH_4$ can also be catalysed by $MgCl_2$ and $MgBr_2$.[54]

Contradictory data have been obtained concerning the catalytic role of amines. When acetone is reduced[70] by $LiBH_4$ and $NaBH_4$ in alcohols and diglyme, it is assumed that the latter do not affect the rate of reaction. On the other hand, under identical conditions (acetone in diglyme + $NaBH_4$) the acceleration of the reaction in the presence of the same triethylamine derivative has been observed.[54]

Among the communications[34,68,72] devoted to the investigation of the kinetics of the reduction of ketones by lithium and sodium tetrahydroaluminates, much attention has been devoted in the paper of Ashby et al.[72] to the investigation of the state of the tetrahydroaluminates in solution in THF. Measurements were made of the dissociation constants of $MAlH_4$ over a wide temperature range and the thermodynamic parameters of the dissociation reaction have been calculated. At 25 °C, $K_D = 6.9 \times 10^{-7}$, 2.1×10^{-7}, and 1.8×10^{-6} mol litre^{-1} for M = Li, Na, and Bu_4N respectively. The temperature dependence of the enthalpy and entropy of dissociation led to the conclusion[72] that the lithium ion pairs $MAlH_4$ are of the solvate-separated type, while the sodium ion pairs are mainly of the contact type.

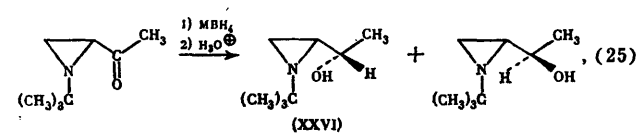
Ashby and Boone[34] used a second-order equation to describe the reactions involving the reduction of mesityl phenyl ketone by $LiAlH_4$ and $NaAlH_4$ in THF. However, this equation is inapplicable[20] if it is assumed[34] that the process takes place with participation of only the free ions or the free ions and the solvate-separated ion pairs.

At 25 °C the observed rate constant for the reaction of mesityl phenyl ketone with $LiAlH_4$ (0.595 litre mol^{-1} s^{-1}) is ten times greater than the rate constant for the reaction with $NaAlH_4$ (0.0587 litre mol^{-1} s^{-1}), which is caused, according to the authors,[34] by the effective activation of the carbonyl group by the lithium cation and not by the difference between the states of the above tetrahydroaluminates in solution. The activation parameters for the reaction of $LiAlH_4$ differ appreciably from the analogous parameters in the case of $NaAlH_4$: $\Delta H^{\neq} = 9.9$ and 17.5 kcal mol^{-1} respectively and $\Delta S^{\neq} = -26.2$ and -5.4 e.u. respectively, which is attributed[34] to the more intense interaction of the ketone with Li^+ in the activated complex.

Under the same conditions as for mesityl phenyl ketone, camphor was reduced[57] by $LiAlH_4$ and $NaAlH_4$. The reaction involving Li^+ is also much faster than that with Na^+, but its kinetic orders with respect to $LiAlH_4$ (1.0) and $NaAlH_4$ (0.73) are different. The authors explain this result by the dimerisation of $NaAlH_4$ (in their view lithium tetrahydroaluminate exists in the monomeric form in THF). However, one should note that the association of ion pairs usually intensifies[20] with decrease of the radius of the alkali metal cation. On the other hand, when the data of Ashby and Boone[34] are used, it is easy to explain the observed kinetic orders with respect to the tetrahydroaluminate. $LiAlH_4$ reacts in the form of free ions and solvate-separated ion pairs (these species usually have[19,20] comparable reactivities) and the order with respect to the tetrahydroaluminate should therefore be close to unity. $NaAlH_4$ is partly dissociated in THF [34] and reacts only in the form of H_4Al^-, so that the order with respect to this reactant should be fractional.[20]

In a study of the reduction of camphor by $LiAlH_4$, Wiegers and Smith[68] made a fairly strange observation: the reaction is retarded by both LiBr and crown polyether. In order to explain this finding, one may suppose that in this instance LiBr not only plays the role of the electrophilic catalyst but also suppresses the dissociation of $LiAlH_4$ via the common ion effect[20] and the latter effect is more important.

Data concerning the influence of the nature of the cation and the solvent on the stereochemistry of the reduction of carbonyl compounds have been obtained in a number of studies. The reaction of tetrahydroaluminates and tetrahydroborates with *N*-t-butylacetyl-2-aziridine, i.e.

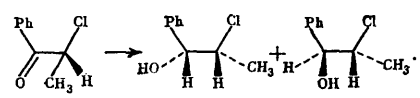


(25)

and the reaction of *N*-t-butyl-2-formylaziridine with methyllithium [cf. Eqn. (11)] result in the formation of two products.[35] In the absence of additives in diglyme, the product (XXVI) predominates (>98 and 92% in the reactions with $LiAlH_4$ and $LiBH_4$ and 80 and 70% in the reactions with $NaAlH_4$ and $NaBH_4$), which is due to the formation of a complex by the alkali metal cation with two heteroatoms of the substrate (see above). The yield of compound (XXVI) is greater in the case of Li^+ than Na^+, which is a consequence of the more effective complex formation with the cation having a smaller radius. In the presence of added cryptands and metal salts in diglyme, the stereochemical result is determined by the cation of the added salt, which indicates a high selectivity in the complex formation reaction of the cryptand. In the reaction involving $LiAlH_4$, together with cryptand 221 + NaI, the yield of compound (XXVI) is the same as in the reaction with $NaAlH_4$ in the absence of additives, while in the reaction with $NaBH_4$ + cryptand 221 + $LiClO_4$ the yield is the same as in the reaction with $LiBH_4$ in the absence of additives.

Since in the reduction of *N*-t-butylacetyl-2-aziridine by $NaBH_4$ in methanol the carbonyl group is activated not only by the alkali metal cation but also (no less effectively) by solvent molecules, the stereoselectivity of the reaction is low: the fraction of the product (XXVI) is about 40%.[35] Only in the presence of large amounts of $LiClO_4$ is it possible to increase the yield of compound (XXVI) to 90%.

The influence of the cation and the solvent on the stereoselectivity of the reduction of α-chloropropiophenone is not very pronounced:[67]



(XXVII)

The yield of compound (XXVII) increases with increase of the solvating capacity of the solvent (on passing from ether to DME) and in DME it diminishes only slightly with increase of the radius of the cation. In almost all cases the yield of compound (XXVII) under identical conditions is slightly higher in the reaction with $MAlH_4$ than in the reaction with MBH_4. The yield of compound (XXVII) is 72% ($LiAlH_4$) and 68% ($LiBH_4$) in ether, and 94% ($LiAlH_4$) and 91% ($LiBH_4$) in the presence of Li^+ and 90% ($NaAlH_4$) and 88% ($NaBH_4$) in the presence of Na^+ in DME. The stereoselectivity is almost the same in DME and methanol: in the reaction with $NaBH_4$, the yields of compound (XXVII) are respectively 88 and 85%. In

both DME and methanol, the composition of the products is independent of the addition of inorganic solvents (LiBr, NaBr).

The reaction conditions, namely the variation of the solvent (ether, DME, methanol) and the cation (Li^+, Na^+) and the addition of LiBr, has the same weak influence on the stereochemistry of the reduction[66] of 4-t-butylcyclohexanone and 2-methylcyclohexanone by alkali metal tetrahydroaluminates and tetrahydroborates. When the former ketone is reduced, the yield of the *cis*-isomer varies in the range 11 to 15%, while in the latter case it varies in the range 22–39%.

The stereochemistry of the reduction of carbonyl compounds has been examined in greater detail in Wigfield's review.[73]

V. CONCLUSION

Analysis of the available literature data on the reactions of organic derivatives of alkali metals and alkali metal tetrahydroborates and tetrahydroaluminates with carbonyl compounds permits the perfectly definite conclusion that the rates of these reactions and the compositions of the products formed can be varied within wide limits by altering the nature of the medium and the metal atom. In certain cases the observed effects permit a quantitative treatment, but usually they can be understood only at a qualitative level, normally by resorting to the idea that the cation is coordinated to the carbonyl oxygen and other heteroatoms. Although the mechanisms of many of the processes investigated have not yet been elucidated in detail owing to the lack of sufficient quantitative data, nevertheless one can already speak of the existence of definite regularities, which may serve as a basis for the successful planning of preparative experiments. Thus it is quite evident that the stereoselectivity can be increased by lowering the polarity of the solvent and by decreasing the size of the alkali metal cation (sometimes by replacing organic derivatives of alkali metals by organomagnesium compounds). The thermodynamic stability of the adduct can be increased by the same procedures and hence its yield can be increased. On the other hand, in order to increase the rate of the nucleophilic addition of the organic derivative of the alkali metal, one must intensify the solvation of the cation, naturally without forgetting at the same time the important role of the cation in the activation of the carbonyl group.

One must assume that further studies on the reactions of organic derivatives of alkali metals with carbonyl compounds, carried out at an effective quantitative level, will permit the final formulation of the idea concerning the role of the various factors in these reactions and hence will make possible certain reliable predictions about the outcome of the process in each specific instance.

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