Influence of Solvent and Cation on the Properties of Oxygen-containing Organic Anions. Part 1. Regioselectivity of Methylation of Acetophenone Enolate

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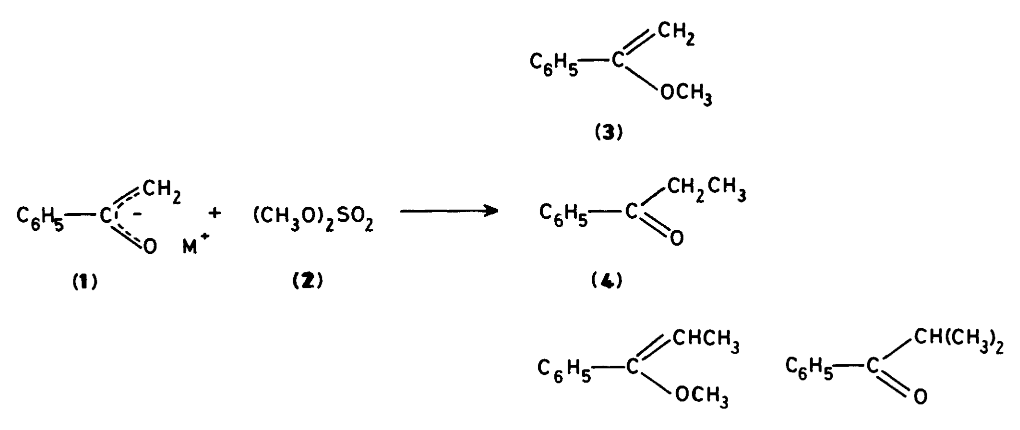
Acetophenone enolates of lithium, sodium, and potassium were methylated with dimethyl sulphate in 14 aprotic solvents. Linear correlations of the logarithm of the molar ratio of *O*-methylation *versus* *C*-methylation products $\log(Q_O/Q_C)$ with solvent polarity and Lewis basicity parameters and either the ionic radius r_M or the reciprocal of the ionic volume (r_M^3) of the metal were found. The results were interpreted with the help of HOMO energies of the enolates, their polarity index q_O/q_C (excess of negative charge densities on O and α-C), and frontier orbital index c_C^2/c_O^2, as a function of the correcting parameter δ_O in HMO calculations which characterizes the action of the cation field upon the electron distribution in the enolate.

Because of the preparative importance of negatively charged ambident nucleophiles, the influence of various variables on their reactivity and regioselectivity has been examined. For the special case of alkali-metal enolates several reviews have been published.[1—4] The influence of solvent and counterion on the regioselectivity of alkali-metal enolates of monoketones has been studied quantitatively in a few cases, although only for a small number of solvents and not for the combination of the effects of both solvent and counterion.

In order to interpret adequately these effects it is, however, also necessary to know the degree of aggregation of the enolates under the same conditions. Conductimetry and ebulliometry have shown[5—7] that sodium enolates of various monoketones, including acetophenone, when dissolved in diethyl ether, do not increase measurably the conductivity of this solvent.[5] Sodiobutyrophenone has a low, though measurable, molar conductance in 1,2-dimethoxyethane, which increases markedly upon addition of solvents with a higher solvating power.[7] The influence of sodiobutyrophenone concentration on molar conductance[7] and the results of ebulliometric studies[6] led to the assumption of an aggregate of three ion pairs of sodiobutyrophenone in diethyl ether[6] and 2.5—2.7 pairs in 1,2-dimethoxyethane.[7] For more polar solvents no such data are available. One can assume, however, that acetophenone alkali-metal enolates are present in dipolar aprotic solvents as neutral ion aggregates (M Enolate)$_n$ with n decreasing as the solvent polarity increases. With increasing solvent polarity small concentrations of charged ion aggregates (M$_{n-1}$ Enolate$_n$)$^-$ and (M$_{n+1}$ Enolate$_n$)$^+$ also begin to appear.

It was also reported that by increasing the polarity of the solvent and the radius of the positive counterion the ^{1}H n.m.r. signal of the α-proton shifts upfield.[8,9] This effect was interpreted as a consequence of more delocalized negative charge in the enolate with increasing solvent polarity and increasing alkali-metal cation radius. The α-^{13}C n.m.r. signals shift upfield under the same conditions; the same effect is achieved by adding crown ethers to the solutions.[10] ^{13}C and ^{7}Li n.m.r. studies[11] show also that lithioisobutyrophenone exists in monodentate ether solvents mainly as tetramer (Li Enolate)$_4$ (with added LiCl as Li$_4$Cl Enolate$_3$), but in 1,2-dimethoxyethane as dimer (Li Enolate)$_2$.

The alkylation of various monoketone enolates has been studied by Zook *et al.*[7] in various aliphatic ethers, either neat or mixed with a more polar aprotic solvent. An increase of the reactivity and of the O:C product ratios (Q_O/Q_C) has been observed with increasing polarity of the medium. In the



$Q_O = Q_3 \quad Q_C = Q_4 + Q_5 + Q_6$

$Q_{Conv} = Q_O + Q_C$

Scheme 1.

Table 1. Conversions in the methylation of acetophenone enolates with dimethyl sulphate at room temperature

Solvent[a]	Cation	Reaction time $(t - t_0)$/min	Conversion (%)[b]
CH_2Cl_2	Li	60	4
CH_2Cl_2	Na	10	10
CH_2Cl_2	K	10	11.5
DG	Li	60	10
DG	Na	10	32
DG	K	10	70
DMF	Li	60	10
DMF	Na	10	33
DMF	K	10	81
HMPA	Li	60	11
HMPA	Na	5	36
HMPA	K	1	81

[a] For the meaning of solvent symbols and experimental conditions see Experimental section. [b] Conversion (%) = $(Q_{\text{conv}})_t \cdot 100/(Q_1)_{t_0}$.

Table 2. C and O methylation products (Q_C and Q_O) and selectivity factors $\log(Q_O/Q_C)$ for the acetophenone enolates with dimethyl sulphate in different solvents

Solvent[a]	Cation	Q_3	Q_4	Q_5	Q_6	$\log(Q_O/Q_C)$
CCl_4	Li	1.7	98.9			−1.770
CH_2Cl_2	Li	8.7	88.3		3.0	−1.022
Toluene	Li	12.9	80.5	1.7	4.9	−0.83
DE	Li	20.9	66.1	6.2	6.8	−0.578
DO	Li	31.3	19.3	28.3	21.1	−0.342
MTHF	Li	35.2	38.7	15.2	10.9	−0.265
THF	Li	36.2	11.6	35.5	16.7	−0.246
DG	Li	36.6	29.0	18.7	15.7	−0.239
DME	Li	36.9	30.6	17.8	14.7	−0.233
HMPA	Li	81.4	15.3	3.3		0.641
CCl_4	Na	14.5	85.5			−0.769
Toluene	Na	28.1	60.0	5.5	6.4	−0.408
DNBE	Na	36.0	59.4	2.5	2.1	−0.250
DE	Na	39.9	40.7	10.4	9.0	−0.178
DO	Na	32.4	55.3	5.2	7.1	−0.319
CH_2Cl_2	Na	39.3	48.3	6.1	6.3	−0.189
MTHF	Na	42.4	35.2	11.3	11.1	−0.133
THF	Na	48.4	31.6	11.1	8.9	−0.028
DG	Na	53.1	40.5	2.4	4.0	0.054
DME	Na	54.8	37.0	4.9	3.3	0.084
DMSO	Na	72.0	20.3	6.3	1.4	0.410
DMA	Na	75.4	9.2	11.3	4.1	0.486
DMF	Na	78.7	20.1	1.3		0.568
HMPA	Na	87.5	10.9	1.6		0.845
CCl_4	K	18.7	46.0	13.0	22.3	−0.638
Toluene	K	31.0	62.8	2.7	3.5	−0.350
DNBE	K	37.8	53.8	2.7	5.8	−0.216
DE	K	44.8	49.4	3.1	2.7	−0.091
DO	K	34.0	18.4	18.8	28.8	−0.288
CH_2Cl_2	K	40.1	57.8	0.9	1.2	−0.175
MTHF	K	53.4	20.0	16.4	10.2	0.059
THF	K	53.4	10.1	22.0	14.5	0.059
DME	K	59.2	10.6	19.5	10.7	0.162
DG	K	58.7	15.7	14.2	11.4	0.153
DMSO	K	73.0	10.0	13.7	3.3	0.432
DMA	K	30.2	4.0	13.4	2.4	0.607
DMF	K	80.0	4.4	12.7	2.9	0.602
HMPA	K	87.8	3.3	8.2	0.7	0.857

[a] For meaning of solvent symbols and experimental details see Experimental section.

alkylation studies of butyrophenone enolates, Zook and Gumby[6] noticed an increase of the reactivity on going from Li^+ to Na^+ and to K^+.

A quantitative treatment of the solvent effect was published by Gompper[1] for the butylation of sodiopropiophenone in five different solvents. A linear correlation between the selectivity factor log (Q_O/Q_C) and the E_T parameter was obtained. Later, Gompper and Vogt[12] mentioned a variation of Q_O/Q_C with the donicity of the solvent.

In this paper we establish an empirical correlation between the regioselectivity and solvent and cation parameters, based on a larger range of experimental results. In order to study the cation and solvent effect on an alkylation reaction, it is desirable to minimize other effects, *e.g.* differences in the steric strain of the different reactive centres in the enolate. Since there are often many predictable products due to polyalkylation and *cis–trans* isomerism it is also important to limit to two the number of reacting centres in the enolate and to exclude the possibility of *cis–trans* isomerism in the alkylation products. These considerations justify the choice of acetophenone enolate in our study.

Published studies on solvent and cation effects in the alkylation of ketone enolates[7,9,12,13] refer to sets of reactions run under different conditions, either because a different alkylation agent was used or a different range of concentrations and method of preparation of the enolate ion were used. It was found to be impossible to establish new quantitative correlations just by evaluating data already published.

In most reports the enolate is obtained by a reaction of a carbonyl compound with alkali-metal t-butylates[13] or other bases. The presence of the respective conjugate acid in the solvent does not allow, however, this result to be regarded as a property of the enolate in neat solvent. This perturbation is greater the less polar is the solvent.

In order to avoid this disadvantage alkali-metal hydrides have to be used.[6] To minimize condensation reactions, the enolate has to be prepared in the presence of alkylating agent.

Results and Discussion

The alkylation of acetophenone enolate with methyl iodide is regiospecific, since there is exclusively alkylation on the carbon atom in all the solvents and cations studied. In contrast the use of dimethyl sulphate as an alkylating agent leads to products resulting from the alkylation of the two reacting centres (Scheme 1). Under these conditions it is possible to study the variation of the regioselectivity with solvent and cation.

Scheme 1 shows the products of primary methylation (**3**) and (**4**) and those resulting from methylation of (**4**), (**5**), and (**6**).

The reactivity, observed for the methylation reaction of (**2**), varies with both the solvent and the alkali-metal hydride. It increases with the polarity of the medium and with radius of the counterion, as shown in Table 1. Since the ratio Q_O/Q_C does not change as the reaction proceeds one can choose, in order to determine the ratio, to lengthen reaction times for lithium and to shorten those for potassium enolate reactions.

Table 2 shows the values, obtained for the quantities expressed in moles, of the *O*-methylation products ($Q_O = Q_3$) and those corresponding to α-*C*-methylation ($Q_C = Q_4 + Q_5 + Q_6$), and the resulting values for the ratio Q_O/Q_C. The precision of the analytical method used in the determination of Q (h.p.l.c. with an internal standard) is $>0.01\%$, but this precision is limited by the reproducibility observed which is *ca.* 0.5%.

The results in Table 2 show a variation in selectivity in the methylation reaction both with the solvent or with the alkali-metal cation. To be able to interpret the variations observed, linear regression analyses of the selectivity factors (log Q_O/Q_C) for the methylation reaction of each acetophenone enolate in different solvents were tried against some empirical solvent

Table 3. Empirical Lewis acidity and basicity parameters for the organic solvents used in this work

Solvent[a]	E_T^N [b]	A_N [c]	Z [d]	π^* [e]	DN	$\Delta\nu_D$ [h]	β [e]	B [i]
Toluene	0.099			0.54	3.4[f]	2	0.11	54
CCl_4	0.055	8.6		0.29	−1.2[f]	−21	0	31
DNBE	0.102		64.0	0.24	18.4[f]	77	0.49	129
DE	0.120	3.9		0.27	19.2[g]	78	0.49	129
DO	0.164	10.8	64.6	0.55	14.8[g]	77	0.39	128
CH_2Cl_2	0.321	20.4	64.2	0.80	0.6[f]	−12	0	43
MTHF	0.179		55.3		18.0[g]	88		
THF	0.207	8.0	58.8	0.58	20.0[g]	90	0.52	145
DME	0.231	10.2	61.2	0.53	24.0[g]	71	0.41	
DG	0.244	9.9	61.5		23.7[g]	69		
DMSO	0.441	19.3	70.2	1.0	29.8[g]	141	0.75	192
DMA	0.401	13.6	66.9	0.88	27.8[g]	113	0.75	178
DMF	0.404	16.0	68.5	0.88	26.6[g]	107	0.71	166
HMPA	0.315	10.6	62.8	0.87	38.8[g]	180	0.99	

[a] For the meaning of solvent symbols and experimental details see Experimental section. [b] Values taken from ref. 14. [c] Values taken from ref. 17 and 20. [d] Values taken from ref. 20 and 21. [e] Values taken from ref. 16. [f] Values taken from ref. 21 (calculated from correlation with $\Delta\nu_D$). [g] Values taken from ref. 17. [h] Values taken from ref. 18. [i] Values taken from ref. 19 and 22.

parameters used in the literature to describe either polarity and Lewis acidity ($X = E_T^N$,[14] Z,[15] π^*,[16] AN[17]) or solvent basicity ($X = \beta$,[16] DN,[17] $\Delta\nu_D$,[18] B[19]).

$$\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_1X \qquad (1)$$

The values of the empirical polarity/Lewis acidity, and basicity parameters for the organic solvents used in the present work[14–22] are shown in Table 3. The results of the regression analysis are shown in Table 4.

Comparison of the regression results shows greater significance for correlations with solvent basicity than with solvent polarity and/or acidity.

Within the set of polarity and/or Lewis acidity parameters correlations are always poor. The one which led by far to the most significant correlation, E_T^N, was selected for a set of planar regressions with the different Lewis basicity parameters reported in Table 5. Regressions with two parameters describe, in general, in a more complete way solvent effects on the selectivity of alkali-metal enolates.

$$\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_2E_T^N + b_2Y \qquad (2)$$

The improvement obtained by changing from a correlation with one of the Lewis basicity parameters to a diparametric correlation including E_T^N is given by the Fisher–Snedecor F test[23] ($F_{imp} > F_{0.01,\,1,\,n-2}$* for a significance level of 99%).

Although the choice of the best basicity parameter Y at this stage is difficult, one can conclude that for lithium the inclusion of E_T^N is not imperative, but for sodium and potassium the improvement obtained with the inclusion of an E_T^N term is very considerable (except for β for potassium where the improvement is less signficant).

Table 4. Parameters of regression analysis leading to correlations for $\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_1X$

X	Cation	log-$(Q_O/Q_C)_0$	a_1	n[a]	R[b]	σ[c]	F[d]
Polarity and/or Lewis acidity parameters							
E_T^N	Li	−1.330	4.39	10	0.607	0.532	4.66
	Na	−0.670	2.909	14	0.837	0.248	28.02
	K	−0.566	2.773	14	0.823	0.249	25.13
A_N	Li	−2.76	−0.019	8	0.128	0.748	0.10
	Na	−0.281	0.031	11	0.333	0.459	1.12
	K	−0.156	0.026	11	0.289	0.449	0.82
Z	Li	−1.945	0.030	6	0.265	0.400	0.30
	Na	−2.372	0.040	10	0.468	0.362	2.24
	K	−1.777	0.032	10	0.385	0.365	1.39
π^*	Li	−1.606	1.908	8	0.573	0.620	2.94
	Na	−0.838	1.386	12	0.779	0.309	15.42
	K	−0.739	1.322	12	0.764	0.310	13.99
Lewis basicity parameters							
DN	Li	−1.258	0.048	10	0.932	0.243	52.93
	Na	−0.624	0.034	14	0.888	0.208	44.62
	K	−5.39	0.033	14	0.896	0.195	48.91
β	Li	−1.231	1.865	8	0.921	0.296	33.40
	Na	−0.594	1.310	12	0.899	0.216	41.91
	K	−0.521	1.281	12	0.903	0.206	44.09
$\Delta\nu_D$	Li	−1.105	0.010	10	0.936	0.235	57.03
	Na	−0.489	0.007	14	0.850	0.238	31.27
	K	−0.405	0.006	14	0.854	0.228	32.30
B	Li	−1.652	0.010	6	0.882	0.294	14.02
	Na	−0.817	0.006	10	0.836	0.251	18.57
	K	−0.745	0.006	10	0.838	0.246	18.83

[a] Number of experimental points. [b] Correlation coefficient. [c] Standard deviation. [d] Fisher parameter.

The cation effect was then accounted for, by introducing in the regression either the Goldschmidt radius r_M Å of the alkali-metal cation, or the reciprocal of r_M^3 corresponding to the ionic volume, as a third parameter, leading to the correlations (3) and (4) with Y = DN, $\Delta\nu_D$, β, or B.

$$\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_3E_T^N + b_3Y + c_3r_M \qquad (3)$$

$$\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_3E_T^N + b_3Y + c_3r_M^{-3} \qquad (4)$$

The use of equations (3) and (4) on the statistical treatment of the data of Table 2 leads to the results shown in Tables 6 and 7. The F values for the two correlations (3) and (4) shown in Tables 6 and 7 indicate that a better description of the cation effect on the selectivity of the methylation reaction of enolates is achieved by using the reciprocal of the ionic volume [model (4)] instead of the ionic radius [model (3)].

The presence of heteroscedasticity and multicollinearity in correlations (3) and (4) was checked by means of tests defined in statistics. The values obtained were compared with adequate distribution functions for the level of significance α.

Bartlett's test[24] for the two correlations gives the value 3.64 which allows the conclusion that both models are homoscedastic (the critical range is [5.99, +∞] for α = 0.05).

The search of multicollinearity was performed by means of Farrar and Glauber's tests.[24] The statistics H_1, which measure the deviation from zero multicollinearity, have values between 12.93 and 15.27 whereas the critical range for α 0.05 is [12.59, +∞] and for 0.01 [16.81, +∞]. These values indicate a small degree of multicollinearity in both models. The statistics H_2, which show if each variable is a linear combination of the others, give values between 0.249 and 6, out of the critical range which is [8.6, +∞] for α 0.05. The statistics H_3 which demonstrate correlations between variables give values <1 for the correlations between E_T^N or Y and r_M or r_M^{-3}, out of the critical range

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* $F_{imp} = (r_{21}^2 - r_{11}^2)\,(n-2)/(1-r_{21}^2)$ where r_{11} = correlation coefficient corresponding to $\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_1Y$, r_{21} = correlation coefficient corresponding to $\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_2E_T^N + b_2Y$, n = number of points, and $F_{0.01,\,1,\,n-2}$ is taken from statistical tables for a significance level of 0.01.

Table 5. Parameters of regression analysis leading to correlations for $\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_2E_T^N + b_2Y$. For the meaning of symbols n, R, σ, and F see caption of Table 4 and for F_{imp} and $F_{0.01,1,n-2}$ see footnote in text

Y	Cation	$\log(Q_O/Q_C)_0$	a_2	b_2	n	R	σ	F	F_{imp}	$F_{0.01,1,n-2}$
DN	Li	−1.440	1.337	0.043	10	0.946	0.232	29.75	2.0	11.3
	Na	−0.808	1.654	0.023	14	0.966	0.122	76.97	25.9	9.33
	K	−0.706	1.503	0.023	14	0.965	0.121	73.68	25.3	9.33
$\Delta\nu_D$	Li	−1.361	1.681	0.009	10	0.960	0.201	40.80	4.6	11.3
	Na	−0.740	1.816	0.004	14	0.953	0.144	53.87	24.3	9.33
	K	−0.637	1.680	0.004	14	0.947	0.147	48.04	19.5	9.33
β	Li	−1.476	1.725	1.644	8	0.945	0.271	20.99	2.5	13.7
	Na	−0.784	1.597	0.904	12	0.969	0.128	69.72	21.4	10.0
	K	−0.699	1.501	0.899	12	0.969	0.126	68.28	5.9	10.0
B	Li	−1.877	1.527	0.009	6	0.919	0.284	8.13	1.7	21.2
	Na	−0.894	1.837	0.003	10	0.969	0.121	53.64	31.5	11.3
	K	−0.817	1.729	0.003	10	0.960	0.135	41.02	23.3	11.3

Table 6. Parameters of regression analysis leading to correlations for $\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_3E_T^N + b_3Y + c_3r$. For the meaning of the symbols n, R, σ, and F see caption of Table 4

Y	$\log(Q_O/Q_C)_0$	a_3	b_3	c_3	n	R	σ	F
DN	−1.667	1.453	0.030	0.670	38	0.932	0.202	74.33
$\Delta\nu_D$	−1.579	1.633	0.006	0.663	38	0.925	0.212	66.81
β	−1.560	1.475	1.153	0.664	32	0.932	0.222	62.27
B	−1.938	1.537	0.005	0.759	26	0.914	0.238	37.21

Table 7. Parameters of regression analysis leading to correlations for $\log(Q_O/Q_C) = \log(Q_O/Q_C)_0 + a_3E_T^N + b_3Y + c_3r^{-3}$. For the meaning of the symbols n, R, σ, F see caption of Table 4

Y	$\log(Q_O/Q_C)_0$	a_3	b_3	c_3	n	R	σ	F
DN	−0.656	1.393	0.030	−0.261	38	0.945	0.182	94.69
$\Delta\nu_D$	−0.579	1.576	0.006	−0.258	38	0.938	0.193	82.85
β	−0.639	1.417	1.145	−0.266	32	0.945	0.198	78.76
B	−0.760	1.477	0.005	−0.315	26	0.935	0.207	51.17

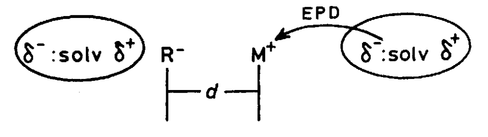
[2.02, +∞] for α 0.05. The values for correlations involving E_T^N and Y lie between 3.83 and 4.22, showing that the small degree of multicollinearity is due to some linear dependence between E_T^N and Y. The presence of multicollinearity may prevent the accurate determination of the relative weights of the different explanatory variables. The approximate values of the weights of the different parameters, as percentages, for the two correlations with either DN or $\Delta\nu_D$ as Lewis basicity parameters are shown in Table 8.

To overcome the problem of multicollinearity it is recommended that an alternative estimation method such as the so-called Principal Component Analysis be carried out. The calculated principal components are rigorously orthogonal but the regression relationship given in terms of the principal components is not easily interpreted since the new explanatory variables are linear combinations of the original ones, not directly identifiable with any magnitude of known physicochemical meaning. In the Appendix, the application of the Principal Components Method to correlations (3) and (4) is illustrated for the single case of the basicity parameter DN. The results show that no significant advantage is gained by using principal components. The slightly higher precision of the relative weights of the components brings too little advantage in order to compensate for the loss of chemical intuition so indispensable for qualitative interpretation of the factors which govern selectivity in enolate alkylation.

The regioselectivity can be considered then to depend on both the solvating power of the solvent and the nature of the metal ion. The high values of $\bar{b}_3$ compared with $\bar{a}_3$ show that, in this case, for the solvating power, electron-pair donation (EPD) characterized by the Lewis basicity parameters Y is about twice as important as the dipolar interaction characterized by E_T^N (since we are dealing only with aprotic solvents E_T^N does not include any contribution from hydrogen bonding). Both the electron pair donation, by partially neutralizing the positive charge of the metal ion, and the dipolar interactions decrease the electrostatic attractive force between enolate and metal ion and hence lengthen the interionic distance d. From the analogy with radical-anions of carbonyl compounds[25] and from n.m.r. studies of enolates[8–10] one can also predict that by increasing the radius r_M of the alkali-metal cation d is lengthened (Scheme 2), which would not be the case with a radical-anion of a hydrocarbon or with a carbanion.

Table 8. Approximate percentage contributions from polarity ($\bar{a}_3$), Lewis basicity ($\bar{b}_3$), and cation ($\bar{c}_3$) effects in correlations (3) and (4)

	Correlation (3)			Correlation (4)		
Y	$\bar{a}_3$	$\bar{b}_3$	$\bar{c}_3$	$\bar{a}_3$	$\bar{b}_3$	$\bar{c}_3$
DN	25	52	23	29	47	24
$\Delta\nu_D$	28	49	23	27	48	25
β	25	52	23	23	52	25
B	31	43	26	29	41	30



Scheme 2.

The increasing nucleophilicity of acetophenone enolate with solvating power and cation radius, as illustrated in Table 2, therefore parallels the increasing average interionic distance in the ion aggregates present. The freer the enolate ion the more reactive it is. The same conclusion can be reached by calculating the energy of the frontier orbital of the enolate. The energy of the highest occupied molecular orbital, HOMO, can be calculated by the Hückel (HMO) method, introducing a correcting parameter δ_O for the oxygen Coulomb integral. Figure 1 shows the HOMO energy plotted against δ_O. According to McClelland[26] the δ_O values are inversely proportional to the distance between the negatively charged oxygen atom and the metal cation. This relation has been used in HMO calculations to account for the effect of a cation on the distribution of the electron spin population in ketyl ion pairs.[26] The results of Figure 1 show

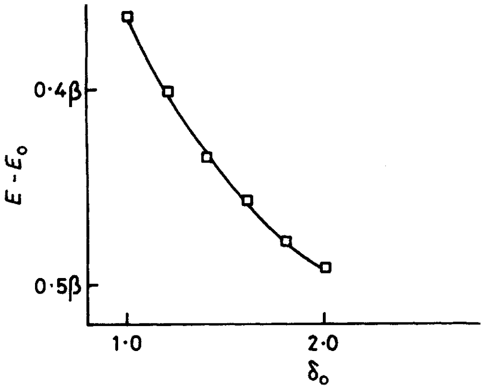


Figure 1. Energy levels for acetophenone enolates calculated by the HMO method as a function of the oxygen Coulomb parameter δ_O

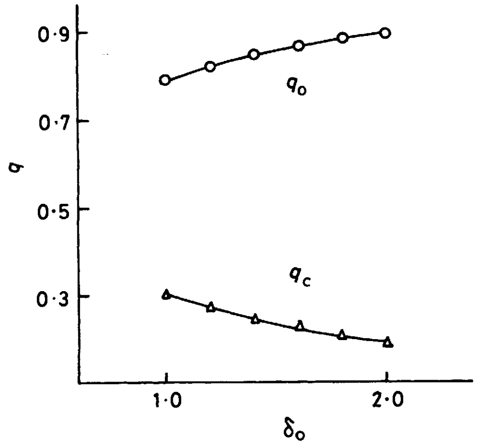


Figure 2. Excess of negative charge density on oxygen (q_O) and on α-carbon atom (q_C) of acetophenone enolate calculated by HMO method as a function of the oxygen Coulomb parameter δ_O

that in the free enolate ion (δ_O 1) the HOMO energy reaches its maximum. It is pulled down by the influence of the positive electric field of a cation in its vicinity (as in a halide [24]). The smaller the distance to the cation the stronger is the effect which increases the energy difference between the HOMO of the enolate and the lowest unoccupied molecular orbital (LUMO) of a substrate of an S_N2 reaction (σ* of the C–X bond, X being the leaving group) and hence decreasing the frontier orbital interaction.

In an attempt to interpret the experimental results on the regioselectivity, Figure 2 shows the calculated excess of negative charge densities q_O on oxygen and q_C on α-carbon of the acetophenone enolate as a function of δ_O. Figure 3 shows the calculated squares of the frontier orbital coefficients for the oxygen atom c_O^2 and for the α-carbon atom c_C^2. The polarity index $P = q_O/q_C$ increases from 2.607 for δ_O 1.0 (free anion) to 4.624 for δ_O 2.0.

If the polarity index was the only determining factor for the Q_O/Q_C product ratio one would expect behaviour for the regioselectivity exactly opposite to what is observed: Q_O/Q_C would be always larger than one and increase with the shortening of the distance to the cation. What is observed experimentally is that Q_O/Q_C is only >1 for relatively free anions. Instead of increasing as the polarity index predicts, Q_O/Q_C decreases the nearer the nucleus of the cation gets to the enolate.

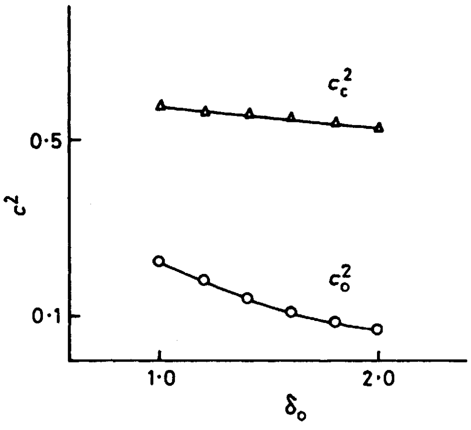


Figure 3. Squares of the atomic coefficients of oxygen (c_O^2) and α-carbon (c_C^2) in the HOMO of acetophenone enolate, calculated by HMO method as a function of the oxygen Coulomb parameter δ_O

If the frontier orbital index c_O^2/c_C^2 was the only factor which determines the regioselectivity, its decrease from 0.398 for δ_O 1.0 (free anion) to 0.133 for δ_O 2.0 would explain the decrease of Q_O/Q_C as the interaction with the cation becomes more important, but it would suggest that always $Q_C > Q_O$, which in reality is only the case when the interionic distance *d* is expected to be shorter (see Table 2, for instance Q_O/Q_C 0.017 for lithium and CCl_4).

The experimental results can, however, be interpreted by assuming that in the free anion the regioselectivity is determined predominantly by the negative charge distribution in the enolate anion and for the shorter interionic distances it is the frontier orbital interaction which controls the product ratio Q_O/Q_C.

Whatever is the most correct theoretical explanation for the experimentally established fact that the free anion is more reactive than the intimate ion association, one has to expect an earlier transition state for the S_N2 reaction of the free anion (nucleophile further away from the methyl carbon), less charge having been transferred when the transition state is reached. Excess of negative charge distribution in the enolate as measured by the polarity index q_O/q_C then becomes the determining factor for the product ratio Q_O/Q_C. In the more highly associated ion aggregates the reactivity is lower and therefore in the later transition state (nucleophile nearer to the methyl carbon) more excess of negative charge has been transferred to the leaving group $CH_3OSO_3^-$. Frontier orbital control as characterized by the frontier orbital index c_O^2/c_C^2 becomes the determining feature, because the initial charge distribution in the enolate has become less relevant for the energy of the transition states of both *O*-and *C*-methylation, favouring *C*-methylation.

In prior publications authors interpreted preferential *C*-alkylation in less polar solvents and with smaller counterions as a shielding effect of the enolate oxygen by the metal cation, which might suggest some kind of steric hindrance. The present interpretation in terms of negative charge *versus* frontier orbital control does, however, not discard this effect because the energy which is necessary to separate the cation from the enolate oxygen is taken into account by considering the lowering of the enolate HOMO energy by the positive field of the counterion. One should also bear in mind that this energy is partially compensated in the transition state by the electrostatic interaction between the growing negative charge on the leaving $CH_3OSO_3^-$ group and another metal cation.

It remains to explain why, when changing from dimethyl sulphate to methyl iodide, exclusive *C*-methylation occurs. The

LUMO energy of the S_N2 reaction substrate (σ^* of the C–X bond, X being the leaving group) becomes much lower with iodide and therefore the HOMO–LUMO interaction term increases to the extent that orbital control dominates completely over charge control in the transition state. This should also imply, according to the Hammond principle, an earlier transition state. One should not, however, be misled by an apparent contradiction with the previous type of analysis by arguing that one would have less negative charge in an earlier transition state transferred to the substrate and therefore the excess of negative charge distribution in the enolate would again become relevant for the selectivity. In order not to be misled one should be aware that lower C–I LUMO and more orbital interaction also mean that in this transition state, which is an earlier one in terms of the nucleophile–substrate distance, much more negative charge has already been transferred to the substrate than in the case where methyl sulphate anion is the leaving group.

It is also important to consider that by comparing the reactivities and selectivities of various acetophenone enolates towards dimethyl sulphate the HOMO energy is lowered by the positive field of the various counterions only by about one-tenth of a β unit at most. Here the earlier transition states correspond to longer enolate–methyl carbon distances and shorter methyl carbon–leaving group distances. In the later transition states the former distance is shorter and the latter longer.

When, however, the LUMO energy of the S_N2 reaction substrate is lowered by changing from C–O to a C–I bond for the same nucleophile to substrate distance, much more extensive electron transfer has taken place already, without necessarily lengthening the C–I bond much more. Whereas the C–O bond cannot receive electrons without extensive bond lengthening, the C–I bond could even, in principle, accept one electron and yield a radical-anion before the bond is actually broken (single-electron transfer). Although there is currently no evidence in this case for a nucleophilic substitution mechanism with a prior single electron-transfer step, the actual transition state may have a C–I bond which is more like that of a radical-anion than in the case of the C–O bond in dimethyl sulphate.

Experimental

Commercial, reagent grade acetophenone and propiophenone were distilled under reduced pressure of argon and dried over molecular sieve 3A (Fluka). Isobutyrophenone was synthesized by Friedel–Crafts reaction from isobutyryl chloride, distilled, and dried in the same way. α-Methoxystyrene and 1-phenyl-1-methoxypropene were synthesized according to the literature[28] from the respective dimethyl acetals also prepared as described.[29] Sodium hydride and lithium hydride were used as supplied by Aldrich. Potassium hydride (Aldrich), suspended in paraffin, was used after washing repeatedly with dry hexane. The traces of hexane remaining from this treatment were drawn off under reduced pressure of argon.

The ethers used as solvents (di-n-butyl ether, DNBE; diethyl ether, DE; 1,4-dioxane, DO; 2-methyltetrahydrofuran, MTHF; tetrahydrofuran, THF; diglyme, DG; 1,2-dimethoxyethane, DME) and toluene (reagent grade) were dried first with lithium tetrahydridoaluminate, distilled, then dried with sodium ribbon, and distilled again under argon into a tube with sodium–potassium alloy. From there it was distilled through a vacuum line directly into the reaction vessel. Carbon tetrachloride CCl_4 and methylene dichloride CH_2Cl_2 were distilled in the vacuum line from tubes, where these solvents had been kept over molecular sieve 3A (Fluka) after distillation under argon.

Other solvents (*NN*-dimethylformamide, DMF; *NN*-dimethylacetamide, DMA; dimethyl sulphoxide, DMSO; hexamethylphosphoroamide, HMPA) were distilled under a reduced pressure of argon, kept over molecular sieve 3A, and added to reaction mixtures with a syringe.

Dimethyl sulphate, DMS, was distilled under reduced pressure of argon, kept over molecular sieve 3A (Fluka), and added with a syringe.

Methylation.—Methylation reactions were all carried out under identical conditions of molar concentration of reagents and temperature in a two-necked flask connected to a vacuum line through a reflux condenser. The alkali-metal hydride (8 mmol) was introduced under argon atmosphere. Solvent (7 ml) was introduced either by distillation as described above or with a syringe. Finally acetophenone (0.480 g, 4 mmol) and dimethyl sulphate (1.00 g, 8 mmol) were introduced under argon.

Product analysis was made by h.p.l.c. with a 10 µm particle size silica gel LiChrosorb, Si60 column of 4 mm inner diameter and 250 mm length. As mobile phase hexane with 0.5% 1,4-dioxane was used. A u.v. detector was tuned to 230 nm.

For the determination of concentrations in analysed solutions of products an internal standard was used.

Appendix

The observed multicollinearity between the explanatory variables E_T^N and either DN, $\Delta\nu_D$, or β, in correlations (3) and (4) may be overcome by the method of factor analysis with a transformation to Principal Components. We refer the application of this method to the set of explanatory variables E_T^N, DN, and either r_M or r_M^{-3}. The aim of the method is the construction out of the initial set of standardized explanatory variables * of new variables (Z_i) called principal components which are linear combinations of the initial explanatory variables and are rigorously orthogonal. The first principal component absorbs and accounts for the largest variation in the set of all explanatory variables, the second one absorbs the maximum of the remaining variation in the variables and so on. The computation required for this analysis was made with a package program of the Scientific Library of IBM.

Table 9 show the results obtained by application of this method to the 38 observations referred in this work with two sets of standardized explanatory variables: $(E_T^N)^s$, $(DN)^s$, $(r_M)^s$ and $(E_T^N)^s$, $(DN)^s$, $(r_M^{-3})^s$.

The principal components calculated were the following:

$$Z_i = \alpha_i(E_T^N)^s + \beta_i(\mathrm{DN})^s + \gamma_i(r_M)^s \quad \text{[for correlation (3)]}$$

$$Z_i = \alpha_i(E_T^N)^s + \beta_i(\mathrm{DN})^s + \gamma_i(r_M^{-3})^s \quad \text{[for correlation (4)]}$$

A regression analysis with the three components Z_1—Z_3 gives relationships (5) and (6) respectively for models (3) and (4).

Table 9. Principal components Z_i and percentage variation λ_i absorbed by each component

	$Z_i = \alpha_i(E_T^N)^s + \beta_i(\mathrm{DN})^s + \gamma_i(r_M)^s$				$Z_i = \alpha_i(E_T^N)^s + \beta_i(\mathrm{DN})^s + \gamma_i(r_M^{-3})^s$			
	α_i	β_i	γ_i	λ_i(%)	α_i	β_i	γ_i	λ_i(%)
Z_1	0.693	0.686	0.223	53.66	−0.687	0.677	0.264	54.16
Z_2	−0.123	−0.192	0.974	39.85	0.143	0.230	0.963	39.42
Z_3	−0.710	0.702	0.048	6.49	−0.712	0.699	−0.061	6.42

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* A standardized variable is obtained by subtracting the average value from each observation and dividing by the standard deviation of the observations.

$$\log(Q_O/Q_C) = -0.093 + 0.383Z_1 + 0.062Z_2 + 0.128Z_3 \quad (5)$$
$$(R\ 0.931;\ F\ 74.31;\ t_1\ 14.606;\ t_2\ 1.823;\ t_3\ 2.492)$$

$$\log(Q_O/Q_C) = -0.093 + 0.386Z_1 - 0.067Z_2 + 0.134Z_3 \quad (6)$$
$$(R\ 0.945;\ F\ 94.77;\ t_1\ 16.463;\ t_2\ -2.196;\ t_3\ 2.907)$$

The Student t values relative to the component Z_1 are 14.61 and 16.46 for correlations (3) and (4) respectively and between 1.8 and 2.9 for the other two components Z_2 and Z_3. The larger the t value the more significant is the regression coefficient of the variable in the regression. For a significance level of 0.01 (99%) the t value must be larger than 2.75, showing that the Z_1 component is far more significant than the other two in correlations (5) and (6). The retention of only one component leads finally to relationships similar to the initial proposed ones.

One can conclude that in the present case there is no advantage in using Principal Component Analysis due to the small degree of multicollinearity between the explanatory variables in the initial models.

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