

Ion Pair Extraction in Preparative Organic Chemistry. X. Kinetic Evidence for the Ion Pair as the Nucleophile in Alkylation of Acetylacetonone and Related Compounds

ARNE BRÄNDSTRÖM

Chemical Research Laboratory, AB Hässle, Fack, S-431 20 Mölndal 1, Sweden

The kinetics of the methylation of some beta-diketones with methyl iodide or dimethyl sulfate has been studied using the 'extractive alkylation' method. It was found that both the anion of the beta-diketone and its ion pair with tetrabutylammonium can function as the nucleophile. Due to the low degree of dissociation of the ion pair in methylene chloride, the ion pair is the dominating nucleophile. Under preparative conditions, it can be regarded as the only nucleophile.

In 1953 Brändström¹ presented a theory for the carbon alkylation of beta-dicarbonyl compounds. According to this theory it is, in modern nomenclature, the chelated ion pair that is the nucleophile in the carbon alkylation reaction. Since then several investigations have been performed which strongly support this theory. However, it still seems to be a controversial question.²

The extractive alkylation process recently introduced by Brändström and Junggren,³ however, provides an excellent opportunity to explore the mechanism of the alkylation reaction. The fundamental points in this reaction are:

1. The reaction between the quaternary ammonium compound of the diketone and the alkylation agent takes place in a two layer suspension where the velocity of the interfacial transport, by proper stirring, can be made very rapid compared to the alkylation reaction.

2. The concentrations (and activities) of the mesomeric anion and the quaternary cation

in the aqueous layer can be readily controlled and measured.

3. By means of simple distribution experiments it is possible to measure, calculate, and predict the concentration of all species of interest in connection with the alkylation.

4. Reaction kinetics can be readily performed at different concentrations of these species and the velocity of the reaction can be correlated to the concentration of the different nucleophiles.

LIST OF SYMBOLS

w and s	= ml of water or solvent layer
L'	= mmol of NaOH added
L	= mmol of NaOH added corrected for the content of OH^- and H_3O^+
A	= total quantity of HA in mmol
Q	= total quantity of Q in mmol
R	= total quantity of RI in mmol
HA	= symbol for weak acid
RI	= symbol for alkylation agent
Q^+	= symbol for tetrabutylammonium
RA	= symbol for alkylated product
$[]_w$	= concentration in aqueous layer, M
$[]_s$	= concentration in organic layer, M
C_{QA}	= total concentration of QA in the solvent, M
K_D	= distribution constant of HA
k'_{HA}	= apparent dissociation constant of HA in water
k^*_{HA}	= apparent dissociation constant of HA defined by eqn. 8
E_{QA}	= extraction constant of QA

E^*_{QA} = apparent extraction constant of QA defined by eqn. 16

E'_{QA} = extraction constant of QA obtained from eqn. 34

$L^0, w^0, s^0, C^0_{QA}, []^0_w, []^0_s$ = values read before RI was added

t_0 = starting time used in calculation

$[RA]_0$ = value of $[RA]_s$ at time $t=t_0$

k_{obs} = observed second order rate constant, $dm^3/mol \text{ min}$

k_A = second order rate constant for the alkylation of the anion, $dm^3/mol \text{ min}$

k_{QA} = second order rate constant for the alkylation of the ion pair, $dm^3/mol \text{ min}$

K_{diss} = thermodynamic dissociation constant of the ion pair

γ_s = mean activity coefficient in the solvent

θ = integral defined by eqn. 31

a_0, a_1, a_2 and a_3 = parameters obtained by the least square fitting of eqn. 33

S.D.(E) S.D.(pH) and S.D.(k) = standard deviations of the quantities E , pH and k obtained

blank experiments. From this we can calculate the quantity L

$$L = L' - w([\text{OH}^-]_w - [\text{H}_3\text{O}^+]_w) \quad (4)$$

we thus have

$$L = w[\text{A}^-]_w \quad (5)$$

From the total quantity A of HA we can deduct

$$A = s[\text{HA}]_s + w[\text{HA}]_w + w[\text{A}^-]_w \quad (6)$$

From eqns. 1, 5, and 6 we obtain

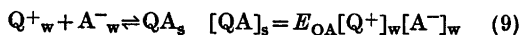
$$[\text{HA}]_w = (A - L)/(sK_D + w) \quad (7)$$

Introducing the values for $[\text{A}^-]_w$ and $[\text{HA}]_w$ into the dissociation equilibrium we obtain

$$k^*_{\text{HA}} = k'_{\text{HA}}/(K_D + w/s) = sL a_{\text{H}_3\text{O}^+}/w(A - L) \quad (8)$$

From this we can calculate the apparent dissociation constant k^*_{HA} used in all calculations in the following.

The extraction of QA follows the following equations:



Using C_{QA} for the concentration of all compounds in the organic layer containing Q and A in the molar portions one to one and supposing that no other combinations of Q and A are formed we obtain for the total quantities L , A and Q

$$L = w[\text{A}^-]_w + sC_{\text{QA}} \quad (10)$$

$$A = w[\text{A}^-]_w + sC_{\text{QA}} + w[\text{HA}]_w + s[\text{HA}]_s \quad (11)$$

$$Q = w[\text{Q}^+]_w + sC_{\text{QA}} \quad (12)$$

A combination of 10 and 12 gives

$$[\text{Q}^+]_w = (Q - L)/w + [\text{A}^-]_w \quad (13)$$

A combination of 1, 10, and 11 gives

$$[\text{HA}]_w = (A - L)/(sK_D + w) \quad (14)$$

$$[\text{HA}]_s = (A - L)K_D/(sK_D + w)$$

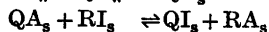
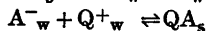
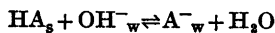
A combination of 2, 8, and 14 gives

$$[\text{A}^-]_w = (A - L)k^*_{\text{HA}}/s a_{\text{H}_3\text{O}^+} \quad (15)$$

The eqns. 15, 13, and 10 enable us to calculate $[\text{A}^-]_w$, $[\text{Q}^+]_w$ and C_{QA} . From these we can calculate an apparent extraction constant E^*_{QA} defined by

METHOD

The reaction studied is of the type



where the subscripts s and w indicate that the ion or molecule is present in the solvent or the water layer. It was followed by registering the quantity of sodium hydroxide added to keep the pH constant during the reaction.

CALCULATIONS

The distribution of HA follows the equations

$$\text{HA}_s \rightleftharpoons \text{HA}_w \quad [\text{HA}]_s = K_D[\text{HA}]_w \quad (1)$$

$$\text{HA}_w + \text{H}_3\text{O}^+ \rightleftharpoons \text{A}^-_w + \text{H}_2\text{O} \quad [\text{A}^-]_w a_{\text{H}_3\text{O}^+} = k'_{\text{HA}}[\text{HA}]_w \quad (2)$$

The total quantity L' of NaOH added is

$$L' = w([\text{A}^-]_w + [\text{OH}^-]_w - [\text{H}_3\text{O}^+]_w) \quad (3)$$

$[\text{OH}^-]_w$ and $[\text{H}_3\text{O}^+]_w$ can be calculated from the pH reading, or better, be determined by

$$E^*_{QA} = C_{QA}/[Q^+]_w[A^-]_w \quad (16) \quad d[RA]_s/dt = k_{obs}C_{QA}[RI]_s \quad (28)$$

The extraction equilibrium during the alkylation can be calculated in the following way. Assume that no side reactions occur such as hydrolysis of the alkylation agent or dialkylation. The following equations are now valid.

$$L = w[A^-]_w + sC_{QA} + s[RA]_s \quad (17)$$

$$A = w[A^-]_w + sC_{QA} + s[RA]_s + w[HA]_w + s[HA]_s \quad (18)$$

$$Q = w[Q^+]_w + sC_{QA} + s[QI]_s \quad (19)$$

$$R = s[RI]_s + s[RA]_s \quad (20)$$

$$[RA]_s = [QI]_s \quad (21)$$

In the same way as before we obtain

$$[Q^+]_w = (Q - L)/w + [A^-]_w \quad (22)$$

$$[A^-]_w = (A - L) k^*_{HA}/s\alpha_{H_3O^+} \quad (23)$$

A combination of 16 and 17 gives

$$s[RA]_s = L - w[A^-]_w - sE^*_{QA}[Q^+]_w[A^-]_w \quad (24)$$

From 20 we obtain

$$[RI]_s = R/s - [RA]_s \quad (25)$$

The eqns. 17 and 22–25 thus provide a possibility of calculating all concentrations of interest in the kinetic measurements if the values of E^*_{AQ} and k^*_{HA} are known. It is, however, not necessary to introduce E^*_{QA} at this point in the calculations since it is readily eliminated in the following way: If the readings at equilibrium prior to the addition of RI are marked with the superscript 0 , we obtain, since $[RA]_s^0 = 0$

$$\frac{C^0_{AQ} = (L^0 - w^0[A^-]_w^0)/s_0 = E^*_{QA}[Q^+]_w^0[A^-]_w^0}{E^*_{QA}[Q^+]_w^0[A^-]_w^0} \quad (26)$$

This is solved for E^*_{QA} which is constant throughout the experiment and therefore can be introduced into eqn. 24 giving

$$s[RA]_s = L - w[A^-]_w - s[Q^+]_w[A^-]_w - (L^0 - w^0[A^-]_w^0)/(s_0[Q^+]_w^0[A^-]_w^0) \quad (27)$$

THE CALCULATION OF THE RATE CONSTANT

During each run the following rate equation has been found to be valid

This is integrated between the limits t and t_0 giving

$$[RA]_s - [RA]_0 = k_{obs} \int_{t_0}^t C_{QA}[RI]_s dt \quad (29)$$

Combining this with 23 and 16 gives

$$[RA]_s - [RA]_0 = (k_{obs} E^*_{QA} k^*_{HA} / \alpha_{H_3O^+}) \int_{t_0}^t (A - L) [Q^+]_w [RI]_s dt / s \quad (30)$$

In this equation the integral

$$\theta = \int_{t_0}^t (A - L) [Q^+]_w [RI]_s dt / s \quad (31)$$

is readily calculated by numerical integration. In fact, the simple trapezoid formula is quite satisfactory. A plot of $[RA]_s$ against θ should give a straight line with the slope α_1

$$\alpha_1 = k_{obs} E^*_{QA} k^*_{HA} / \alpha_{H_3O^+} \quad (32)$$

from which k_{obs} can be calculated.

In some cases when the reaction was allowed to proceed to more than 20 % conversion, the lines were slightly curved, especially when disubstitution was possible. It was, however, never difficult to obtain the slope at the time $t=0$ which is that of primary interest.

Due to the rather extensive amount of numeric calculations involved in the determination of each velocity constant, a computer program was constructed. In order to calculate the value for the slope of the plot of $[RA]_s$ against θ , the curve was fitted with a polynomial of the type

$$[RA]_s = a_0 + a_1\theta + a_2\theta^2 + a_3\theta^3 \quad (33)$$

The parameters a_0 , a_1 , a_2 , and a_3 were determined by the method of least square, minimizing the error in $[RA]_s$. In all runs the fit was excellent. The slope at $t=t_0$ is equal to α_1 which is obtained accurately in this way.

In order to cover as wide a concentration range as possible, it became necessary to study both rapid and slow reactions. The slow reactions, down to 2 % conversion in 24 h, presented no problems other than trivial mechanical ones such as performing very rapid stirring in a closed system for a long period.

The rapid reactions (20 % conversion in less than 10 min) raised two additional complications, however. The first one was that the velocity was sometimes controlled by the rate of the interfacial transport. When this occurred, the needle of the pH meter showed small and rapid fluctuations in time with additions of the base. In the cases where this could not be avoided by increasing the rate of stirring, the experiment was rejected. The second complication arose from the construction of the instrument. In the most rapid reactions the instrument could not keep the pH at the same level as that at equilibrium. This was seen by a slight S shape of the plot of L' against t presented by the instrument. A pH was also read on the instrument that was slightly lower than that at equilibrium. This problem was handled in the following way.

The time $t=0$ for the addition of the alkylation agent was marked on the t axis of the plot of L' against t presented by the instrument. The first part of the curve, before the pH had been stabilized, was replaced by a line obtained by back extrapolating the curve to $t=0$. The calculation was then performed in the usual way.

RESULTS AND DISCUSSIONS

The dissociation constant of acetylacetone in 0.5 M Na_2SO_4 was determined in the usual way giving $\text{pk}'_{\text{HA}}=8.81$. The determination of the apparent dissociation constant k^*_{HA} in the two layer system, methylene chloride and 0.5 M Na_2SO_4 , presented no problem. Five

titration curves with the starting concentration of HA ranging from 0.1 to 0.5 M gave $\text{pk}^*_{\text{HA}}=10.42$. $\text{S.D.}(\text{pk})=0.016$.

The determinations of the apparent extraction constants E^*_{QA} were performed in rather concentrated solutions. The transport of matter from one layer to the other thus resulted in a slight change in the volumes s and w . Control experiments gave the result that, within the experimental errors, the change in volume expressed in ml was identical to the weight of the transported matter in grams. s and w were therefore corrected in accordance with this.

A typical run for the determination of the apparent extraction constant E^*_{QA} of tetrabutyl ammonium acetylacetonate is given in Table 1 and the results of 5 such runs are given in Table 2.

The constants obtained can be summarized by the formula

$$E'_{\text{QA}} = 5.43 + 0.128A \quad (34)$$

The small but highly significant variation of E'_{QA} with A is best interpreted as a medium effect. A solution containing HA or QA in methylene chloride is a better extraction solvent for QA than pure methylene chloride. Every attempt to correlate the variation of E^*_{QA} with the formation of species such as $(\text{QA})_2$ and QAHA gave, as a result, such low formation constants of these species that their physical significance is highly questionable.⁴ There is thus no reason to introduce species other than the ion pair AQ (and the free anion A^-) in the kinetical discussions.

Table 1. Determination of the apparent extraction constant E^*_{QA} of tetrabutylammonium acetylacetonate. $A=2.5$, $Q=12.5$, $\text{NaOH}=5.095$, $s_0=25$, $w_0=25$, $t=25^\circ\text{C}$.

ml	L	pH	w	s	$[\text{A}^-]_w$	$[\text{Q}^+]_w$	C_{QA}	$E^*_{\text{QA}}^a$
0.05	0.255	8.92	25.02	25.03	0.00284	0.493	0.00734	5.24
0.10	0.510	9.28	25.03	25.07	0.00579	0.484	0.01457	5.20
0.15	0.764	9.50	25.04	25.11	0.00839	0.477	0.02206	5.51
0.20	1.019	9.70	25.06	25.14	0.01135	0.470	0.02922	5.48
0.25	1.269	9.86	25.06	25.19	0.01366	0.461	0.03678	5.84
0.30	1.524	10.04	25.07	25.23	0.01642	0.454	0.04408	5.91
0.35	1.773	10.23	25.08	25.26	0.01897	0.447	0.05136	6.06
0.40	2.023	10.48	25.10	25.30	0.02216	0.439	0.05797	5.96

^a $E^*_{\text{QA}}=5.65$, $\text{S.D.}(E)=0.31$.

Table 2. The apparent extraction constant E^*_{QA} of tetrabutylammonium acetylacetonate. $E'_{QA} = 5.43 + 0.1284A$; $Q = 12.5$.

A	ml	pH	E^*_{QA}	Mean	S.D.(E)	E'_{QA}
2.5	0.05	8.92	5.24			
2.5	0.10	9.28	5.20			
2.5	0.15	9.50	5.51			
2.5	0.20	9.70	5.48			
2.5	0.25	9.86	5.84			
2.5	0.30	10.04	5.91			
2.5	0.35	10.23	6.06			
2.5	0.40	10.48	5.96	5.65	0.31	5.75
5.0	0.10	8.88	5.99			
5.0	0.20	9.24	6.03			
5.0	0.30	9.48	6.11			
5.0	0.40	9.69	5.96			
5.0	0.50	9.87	6.05			
5.0	0.60	10.05	6.23			
5.0	0.70	10.25	6.33			
5.0	0.80	10.50	6.42	6.14	0.16	6.07
7.5	0.15	8.85	6.69			
7.5	0.30	9.22	6.60			
7.5	0.45	9.48	6.27			
7.5	0.60	9.69	6.31			
7.5	0.75	9.88	6.32			
7.5	0.90	10.07	6.41			
7.5	1.05	10.28	6.44			
7.5	1.20	10.52	6.92	6.50	0.21	6.39
10.0	0.20	8.85	6.67			
10.0	0.40	9.22	6.78			
10.0	0.60	9.48	6.64			
10.0	0.80	9.69	6.69			
10.0	1.00	9.89	6.62			
10.0	1.20	10.09	6.60			
10.0	1.40	10.29	7.05	6.73	0.14	6.71
12.5	0.25	8.83	7.30			
12.5	0.50	9.22	7.00			
12.5	0.75	9.49	6.74			
12.5	1.00	9.70	6.93			
12.5	1.25	9.90	6.97			
12.5	1.50	10.11	6.85			
12.5	1.75	10.33	6.93			
12.5	2.00	10.60	6.95	6.96	0.19	7.04

In the following E'_{QA} obtained from eqn. 34 is used instead of E^*_{QA} in eqn. 32 in the calculation of k_{obs} .

Some remarks must be made, however, concerning the use of eqn. 34. It has been obtained from measurements in the concentration range 0.007–0.25 M in $[QA]_s$. In this concentration range the dissociation of $[QA]_s$ into Q^+ and A^- in the organic layer can be expected to be very low and its influence on

E^*_{QA} can be neglected. From the discussion above, it is obvious that eqn. 34 is obtained in the concentration region where $C_{QA} = [QA]_s$ and E'_{QA} thus connects the concentrations in both layers by the equation

$$[QA]_s = E'_{QA}[Q^+]_w[A^-]_w \quad (35)$$

When E'_{QA} is used instead of E^*_{QA} to calculate k_{obs} by eqn. 32, it follows from the deductions of eqn. 30 that C_{QA} in eqn. 28

has to be replaced by $[QA]_s$. These are, however, the only points where the use of E'_{QA} affects the calculations.

In this connection, it should be pointed out that there seems to be no method available at present to determine E^*_{QA} in the concentration range where the dissociation is of importance. The present method is too inaccurate in this concentration range and the reactivity of QA towards methylene chloride is too high to allow accurate measurements by other, more time consuming methods.

The kinetic measurements of the methylation of acetylacetone with methyl iodide in the presence of tetrabutylammonium ions have been performed at different pH values (5.5–9.0), different initial concentration of acetylacetone (0.04–0.5 M) and of tetrabutylammonium ions (0.1–0.5 M). A typical run is given in Table 3 and the results of 41 runs of this type are given in Table 4.

The k_{obs} values from different runs, but under the same conditions may differ by up to 10 % from the mean value. This can be explained by considering the difficulties in determining the pH values in the different runs. From the calculation of k^*_{HA} , we can

see that the standard deviation in the pK determination is about 0.016 pK unit. This corresponds to a standard deviation in the pH readings of 0.016 pH units and in k_{obs} of about 3.7 %. This is in good agreement with mean standard deviation in k_{obs} of 4.2 % found by experiment.

From Table 4, we can see that k_{obs} is fairly constant (within a factor of 2) in all experiments in spite of the fact that C_{QA} is varied within a factor of 3000. This is in good agreement with the assumption that the ion pair QA is the dominating nucleophile. (In the calculations it was assumed that the velocity is proportional to C_{QA} and from the equilibrium studies it was demonstrated that $C_{QA} \approx [QA]_s$).

A careful inspection of the kinetic runs made at pH 9 (Run 17–41) reveals that k_{obs} is independent of the value of Q and almost independent of the value of A . The small decrease in k_{obs} with an increasing $[HA]_s$ is probably a medium effect. Thus an increase in $[HA]_s$ slightly increases the extraction and at the same time makes the ion pair less reactive toward methyl iodide.

Table 3. Methylation of acetylacetone with methyl iodide at pH 8.98. $A=7.5$, $Q=2.5$, $R=16.07$, $s=s^0=26.0$, $w=25.0$, $L^0=0.492$.

$t-t_0$ min	L	$\theta \times 10^2$	$[RA]_{calc}$ $\times 10^2$ ^a	$[RA]_{found}$ $\times 10^2$
0	0.515	0	0.103	0.105
0.25	0.542	0.359	0.224	0.223
0.50	0.568	0.712	0.346	0.344
0.75	0.595	1.057	0.465	0.464
1.00	0.622	1.396	0.585	0.587
1.25	0.648	1.729	0.705	0.704
1.50	0.674	2.055	0.823	0.822
1.75	0.700	2.374	0.940	0.938
2.00	0.726	2.688	1.055	1.055
2.25	0.752	2.995	1.171	1.073
2.50	0.777	3.296	1.286	1.288
2.75	0.802	3.591	1.398	1.401
3.00	0.827	3.880	1.511	1.509
3.25	0.851	4.164	1.622	1.619
3.50	0.876	4.442	1.732	1.730
3.75	0.900	4.715	1.840	1.840
4.00	0.925	4.982	1.949	1.950
4.25	0.948	5.244	2.055	2.054
4.50	0.973	5.501	2.160	2.161

^a $a_0=0.001031$; $a_1=0.3352$; $a_2=0.7232$; $a_3=-0.3409$; $[RA]_{calc}=a_0+a_1\theta+a_2\theta^2+a_3\theta^3$.

Table 4. Methylation of acetylacetone with methyl iodide.

pH	A	Q	$\alpha_{\text{HO}^+}/k_{\text{HA}}^*$	E'_{QA}	$1000\alpha_1$	k_{obs}	Mean	S.D.(k)	Exp. No.
5.50	12.5	2.5	83180	7.04	0.2277	2.69	2.69		1
6.00	12.5	2.5	26300	7.04	0.5659	2.11	2.11		2
6.50	12.5	2.5	8318	7.04	1.618	1.91	1.91		3
7.00	12.5	2.5	2630	7.04	4.493	1.68			4
7.00	12.5	2.5	2630	7.04	4.579	1.71	1.70	0.02	5
7.50	12.5	2.5	831.8	7.04	13.59	1.61			6
7.50	12.5	2.5	831.8	7.04	13.58	1.61			7
7.50	12.5	2.5	831.8	7.04	14.60	1.73			8
7.50	12.5	2.5	831.8	7.04	13.25	1.57	1.63	0.07	9
8.00	12.5	2.5	263	7.04	40.45	1.51			10
8.00	12.5	2.5	263	7.04	34.59	1.29			11
8.00	12.5	2.5	263	7.04	38.43	1.44			12
8.00	12.5	2.5	263	7.04	41.95	1.57	1.45	0.12	13
8.48	12.5	2.5	87.1	7.04	100.6	1.24			14
8.48	12.5	2.5	87.1	7.04	113.6	1.41			15
8.50	12.5	2.5	83.2	7.04	135.2	1.60	1.42	0.18	16
9.00	1.0	2.5	26.3	5.56	337.9	1.60	1.60		17
9.00	1.5	2.5	26.3	5.62	337.1	1.58	1.58		18
9.00	2.5	2.5	26.3	5.75	342.7	1.57			19
9.00	2.5	2.5	26.3	5.75	323.6	1.48	1.53	0.06	20
8.99	5.0	2.5	26.92	6.07	346.5	1.54			21
9.00	5.0	2.5	26.30	6.07	312.4	1.35	1.45	0.13	22
8.98	7.5	2.5	27.54	6.39	335.2	1.44			23
9.00	7.5	2.5	26.30	6.39	331.6	1.36	1.40	0.06	24
8.98	10.0	2.5	27.54	6.71	345.4	1.42			25
9.00	10.0	2.5	26.30	6.71	340.4	1.33	1.38	0.06	26
8.97	12.5	2.5	28.18	7.04	333.4	1.33			27
9.00	12.5	2.5	26.30	7.04	369.1	1.38			28
8.99	12.5	2.5	26.92	7.04	371.2	1.42			29
8.96	12.5	2.5	28.84	7.04	349.0	1.43	1.39	0.05	30
9.00	2.5	5.0	26.30	5.75	303.2	1.39			31
9.00	2.5	5.0	26.30	5.75	319.9	1.46	1.43	0.05	32
8.97	2.5	7.5	28.18	5.75	291.0	1.43			33
8.98	2.5	7.5	27.54	5.75	303.8	1.46			34
9.00	2.5	7.5	26.30	5.75	304.5	1.39	1.43	0.04	35
8.97	2.5	10.0	28.18	5.75	273.8	1.34			36
8.97	2.5	10.0	28.18	5.75	278.1	1.36			37
9.00	2.5	10.0	26.30	5.75	345.0	1.56	1.42	0.12	38
8.96	2.5	12.5	28.84	5.75	295.1	1.48			39
8.96	2.5	12.5	28.84	5.75	274.8	1.38			40
9.00	2.5	12.5	26.30	5.75	328.6	1.50	1.45	0.06	41

Still more interesting results were obtained by varying the pH (Run 1–16 and 27–30). We can observe a small but statistically highly significant increase in k_{obs} with a decrease in pH. The greatest increase in k_{obs} for a given decrease in pH can be observed in the solutions with the lowest concentration C_{QA} . In these solutions we can expect the most extensive dissociation of the ion pair. It is therefore natural to consider the possibility that both the ion pair and the free anion can function as the nucleophile. If we assume

that both the anion and the ion pair react with RI by second order kinetics we obtain the total reactions rate

$$d[\text{RA}]_s/dt = (k_{\text{A}}[\text{A}^-]_s + k_{\text{QA}}[\text{QA}]_s) [\text{RI}]_s \quad (36)$$

From the discussion given in connection with the use of eqn. 34 it follows that this should be equal to that obtained from the modified eqn. 28

$$d[\text{RA}]_s/dt = k_{\text{obs}}[\text{QA}]_s [\text{RI}]_s \quad (37)$$

we thus obtain

$$k_{\text{obs}} = k_{\text{QA}} + k_{\text{A}}[\text{A}^-]_{\text{s}}/[\text{QA}]_{\text{s}} \quad (38)$$

In the organic layer we have at $t=0$, $[\text{Q}^+]_{\text{s}} = [\text{A}^-]_{\text{s}}$ and the dissociation equilibrium in the organic layer gives

$$(\gamma_{\text{s}})^2[\text{A}^-]_{\text{s}}^2 = K_{\text{diss}}[\text{QA}]_{\text{s}} \quad (39)$$

where γ_{s} is the mean activity coefficient of the ions in the solvent and K_{diss} the dissociation constant of the ion pair. From 38 and 39 we obtain.

$$k_{\text{obs}} = k_{\text{QA}} + k_{\text{A}}(K_{\text{diss}}/[\text{QA}]_{\text{s}})^{1/2}/\gamma_{\text{s}} \quad (40)$$

A plot of k_{obs} against $1/\gamma_{\text{s}}[\text{QA}]_{\text{s}}^{1/2}$ should thus give a straight line with the intercept k_{QA} and the slope $k_{\text{A}}(K_{\text{diss}})^{1/2}$. In the present investigation the concentration $[\text{QA}]_{\text{s}}$ is in the range 10^{-2} – 10^{-5} ,⁴ and the dissociation constant K_{diss} can be estimated to be not much higher than 10^{-5} . In this case γ_{s} will be close to unity and a good approximation of its value can be obtained by the formula of Marshall and Grünwald⁵ using $K_{\text{diss}} = 10^{-5}$ as an approximative value of this constant. The value of $[\text{QA}]_{\text{s}}$ is obtained from 35 (9 with $E'_{\text{QA}} = E_{\text{QA}}$).

The results of a least square calculation according to eqn. 40 are given in Table 5. We can see that k_{obs} is very close to k_{calc} which means that the fit of eqn. 40 is very good. In fact, the difference $k_{\text{obs}} - k_{\text{calc}}$ is of the same magnitude as the standard deviation of the k_{obs} values used in the calculation. The results obtained thus strongly support the assumption

that both the anion and the ion pair are nucleophiles in the methylation of acetylacetone with methyl iodide by the process "extractive alkylation". Under preparative conditions, the reaction is almost exclusively an alkylation of the ion pair.

Eqn. 40 gives k_{QA} directly. For the calculation of k_{A} a knowledge of K_{diss} is necessary. This is not available by experiments. From the magnitude of the dissociation constants of other tetrabutylammonium salts,¹¹ we can make a rough guess or estimate $K_{\text{diss}} \approx 10^{-5}$. Using this value we can see that k_{A} is of the same magnitude as k_{QA} . Due to the low degree of dissociation, the dominating reaction, however, will be that of the ion pair.

This result is in direct contrast to the results obtained by Kurts *et al.*³ for the alkylation of alkali salts of ethyl acetoacetate with ethyl tosylate in hexamethylphosphortriamide in which no ion pair reactivity could be detected. This difference might be explained by the differences in size of the cation⁹ and by differences in the solvation of the cation part of the ion pair.¹⁰ An increase in the distance between the two charged centres can be expected to increase the reactivity of the anion part of the ion pair. The same effect can also be expected from a better solvation of the cation part of the ion pair.

The methylation of acetylacetone with dimethyl sulfate, the methylation of methylacetylacetone with methyl iodide, and the methylation of benzoylacetone with methyl iodide were also studied.

Table 5. Methylation of acetylacetone with methyl iodide. Summary of results. $A=12.5$, $Q=2.5$, $R=16.07$, 25.0°C .

pH	$[\text{OA}]_{\text{s}} \times 10^3$	γ_{s}	$1/\gamma_{\text{s}}[\text{QA}]_{\text{s}}^{1/2}$	k_{obs}	k_{calc}^a	% ion pair reaction
5.50	0.00423	0.99	491	2.69	2.70	53
6.00	0.0134	0.98	279	2.11	2.15	68
6.50	0.0418	0.98	158	1.91	1.83	78
7.00	0.131	0.97	90	1.70	1.65	86
7.50	0.414	0.96	51	1.63	1.55	92
8.00	1.28	0.95	29	1.45	1.50	95
8.50	3.68	0.93	18	1.42	1.47	97
9.00	9.99	0.91	11	1.39	1.44	99

^a $k_{\text{QA}} = 1.42$, S.D. = 0.03; $k_{\text{A}}(K_{\text{diss}})^{1/2} = 2.62 \times 10^{-3}$; S.D. = 0.13×10^{-3} ; $k_{\text{calc}} = k_{\text{QA}} + k_{\text{A}}(K_{\text{diss}}/[\text{QA}]_{\text{s}})^{1/2}/\gamma_{\text{s}}$.

Table 6. Methylation of acetylacetone with dimethyl sulfate. $A = 12.5$, $Q = 2.5$, $R = 10.58$, 25.0°C , $E'_{\text{QA}} = 7.04$.

pH	$\alpha_{\text{H}_3\text{O}^+}/k^*_{\text{HA}}$	γ_s	a_1	$[\text{QA}]_s$	k_{obs}	k_{calc}^a
7.00	2630	0.97	0.00847	1.31×10^{-4}	3.16	3.22
7.50	831.8	0.96	0.02392	4.14×10^{-4}	2.83	2.69
8.00	263	0.95	0.06401	1.28×10^{-3}	2.39	2.40
8.47	89.1	0.93	0.1691	3.68×10^{-3}	2.14	2.25
9.00	26.3	0.91	0.5882	9.99×10^{-3}	2.20	2.16

^a $k_{\text{QA}} = 2.01$; S.D. = 0.08; $k_{\text{A}}(K_{\text{diss}})^{1/2} = 13.4 \times 10^{-3}$; S.D. = 1.7×10^{-3} ; $k_{\text{calc}} = k_{\text{QA}} + k_{\text{A}}(K_{\text{diss}}/[\text{OA}]_s)^{1/2}/\gamma_s$.

Table 7. Determination of the apparent extraction constant E^*_{QA} of tetrabutylammonium methylacetylacetonate. $A = 2.5$, $Q = 12.5$, $\text{NaOH} = 1.017$, $s = 25$, $p k^*_{\text{HA}} = 12.41$, $p k'_{\text{HA}} = 10.76$.

ml	L	pH	w	$[\text{A}^-]_w$	$[\text{Q}^+]_w$	C_{QA}	E^*_{QA}	E'_{QA}^a
0.50	0.361	10.97	25.50	0.00310	0.479	0.01133	7.61	7.69
0.75	0.591	11.23	25.75	0.00504	0.468	0.01860	7.88	7.85
1.00	0.823	11.43	26.00	0.00702	0.456	0.02590	8.08	8.01
1.25	1.048	11.60	26.25	0.00900	0.445	0.03293	8.23	8.16
1.50	1.264	11.76	26.50	0.01107	0.435	0.03949	8.20	8.31
1.75	1.463	11.90	26.75	0.01282	0.425	0.04570	8.39	8.44
2.00	1.655	12.03	27.00	0.01409	0.416	0.05211	8.89	8.59
2.25	1.798	12.17	27.25	0.01616	0.409	0.05576	8.44	8.67

^a $E'_{\text{QA}} = 7.44 + 22.0 C_{\text{QA}}$

Table 8. Methylation of methylacetylacetone with methyl iodide. $A = 2.5$, $R = 16.07$, $p k^*_{\text{HA}} = 12.41$, 25.0°C .

pH	Q	$\alpha_{\text{H}_3\text{O}^+}/k^*_{\text{HA}}$	E'_{QA}	$a_1 \times 10^3$	$[\text{QA}]_s \times 10^5$	γ_s	$1/\gamma_s[\text{QA}]_s^{1/2}$	k_{obs}	k_{calc}^a
8.50	2.5	8130	7.44	1.003	0.909	0.99	335	1.10	1.09
8.50	12.5	8130	7.44	0.958	4.55	0.98	151	1.05	0.97
9.00	2.5	2570	7.44	2.707	2.82	0.98	192	0.94	0.99
9.50	2.5	813	7.44	8.055	8.84	0.97	110	0.88	0.94
10.00	2.5	257	7.44	26.11	27.2	0.96	63	0.91	0.91
10.00	12.5	257	7.47	26.58	135	0.95	29	0.91	0.89

^a $k_{\text{QA}} = 0.87$, S.D. = 0.03; $k_{\text{A}}(K_{\text{diss}})^{1/2} = 0.65 \times 10^{-3}$, S.D. = 0.15×10^{-3} ; $k_{\text{calc}} = k_{\text{QA}} + k_{\text{A}}(K_{\text{diss}}/[\text{QA}]_s)^{1/2}/\gamma_s$.

The apparent extraction constants E^*_{QA} for the tetrabutylammonium salts of methylacetylacetone and benzoylacetone were not investigated as carefully as that for acetylacetone. Even in these cases E^*_{QA} showed a slight variation with the composition of the organic layer, but the variation was too low to be interpreted as the formation of any other species than the ion pair and the anion. For

interpolation purposes the formulas given for E'_{QA} at the bottom of Tables 7 and 9 were used. They fit the experimental values very nicely, but should not be used for any other purpose than interpolations.

In the methylation with dimethyl sulfate a slight complication occurs. Besides the main reaction there is a slow pH independent hydrolysis of dimethyl sulfate. This is readily cor-

Table 9. Determination of the apparent extraction constant E^*_{QA} of tetrabutylammonium benzoyl acetate. $A = 2.5$, $Q = 12.5$, $\text{NaOH} = 1.017$, $s = 25$, $\text{p}k^*_{\text{HA}} = 12.37$.

ml	L	pH	w	$[\text{A}^-]_{\text{w}} \times 10^5$	$[\text{Q}^+]_{\text{w}}$	C_{QA}	E^*_{QA}	E'_{QA}^a
0.25	0.2441	8.82	25.25	2.54	0.485	0.00974	790	775
0.50	0.4780	9.15	25.50	4.87	0.471	0.01907	831	822
0.75	0.7160	9.38	25.75	7.30	0.458	0.02856	854	869
1.00	0.9580	9.55	26.00	9.34	0.444	0.03822	922	916
1.25	1.1985	9.72	26.25	11.65	0.431	0.04782	953	964
1.50	1.4396	9.88	26.50	13.73	0.418	0.05744	1002	1012
1.75	1.6796	10.06	26.75	16.07	0.405	0.06701	1030	1059
2.00	1.9211	10.25	27.00	17.57	0.392	0.07665	1113	1107
2.25	2.1601	10.52	27.25	19.21	0.380	0.08619	1182	1154

$$^a E'_{\text{QA}} = 727 + 4953 C_{\text{QA}}$$

Table 10. Methylation of benzoylacetone with methyl iodide. $A = 2.5$, $Q = 2.5$, $R = 16.07$, $\text{p}k^*_{\text{HA}} = 12.37$; 25.0 °C.

pH	$\alpha_{\text{H}_2\text{O}^-}/k^*_{\text{HA}}$	E'_{QA}	a_1	$[\text{QA}]_{\text{s}} \times 10^4$	γ_{s}	$1/\gamma_{\text{s}}[\text{QA}]_{\text{s}}^{1/2}$	k_{obs}	k_{calc}^a
8.00	23440	728	0.0341	3.08	0.96	59.4	1.098	1.097
8.50	7413	732	0.1027	9.52	0.95	34.1	1.040	1.049
9.00	2344	742	0.3296	29.66	0.93	19.7	1.041	1.022
9.50	741	769	1.034	85.44	0.91	11.9	0.997	1.008

$$^a k_{\text{QA}} = 0.985, \text{S.D.} = 0.017; k_{\text{A}}(K_{\text{diss}})^{1/2} = 1.88 \times 10^{-3}, \text{S.D.} = 0.46 \times 10^{-3}; k_{\text{calc}} = k_{\text{OX}} + k_{\text{A}}(K_{\text{diss}}/[\text{QA}])^{1/2}/\gamma_{\text{s}}$$

rected for, however. In the other reactions no complication occurred. The results are given in Tables 6–10.

All these reactions behaved in the same way, indicating that the ion pair is the dominating nucleophile, but some alkylation of the free ion also occurs. The results are summarized in Table 11. It is interesting to note that both the carbon alkylation with methyl iodide and the oxygen alkylation with dimethyl sulfate follow the same type of kinetics.

From the rather uncertain $k_{\text{A}}(K_{\text{diss}})^{1/2}$ values it can be concluded that the reaction of the anion seems to be somewhat more important for the oxygen alkylation with dimethyl sulfate than for the carbon alkylation with methyl iodide.

The interesting question as to whether the oxygen and carbon alkylation are using the same nucleophile or not, was also studied in another way. The isopropylation of the tetrabutylammonium salt of acetylacetone with isopropyl iodide in methylene chloride gives

almost equal quantities of *C*- and *O*-alkylation. Assume that the free anion takes part in the oxygen alkylation to a different extent than in the carbon alkylation and that the reaction with the anion is of significant importance for the formation of at least one of the products. A change in the degree of dissociation should then influence the product composition. Due to the common ion effect, the addition of QI to the mixture should depress the dissociation of QA. The addition of a large amount of QI to the isopropylation reaction solution had no effect on the product composition.

The anion, therefore, is of the same, or of very little importance for both the carbon and oxygen alkylation in this case.

EXPERIMENTAL

The solution of tetrabutylammonium sulfate was prepared by careful neutralisation of pure tetrabutylammonium hydrogen sulfate with carbonate free sodium hydroxide. The absence

Table 11. The alkylation of tetrabutylammonium salts of some β -diketones. Summary.

β -Diketone ^a	Alkylating agent	k_{QA}	S.D.	$k_A(K_{diss})^{1/2} \times 10^3$	S.D. $\times 10^3$	Type of alkylation
I	CH ₃ I	1.42	0.03	2.62	0.13	C
I	(CH ₃) ₂ SO ₄	2.01	0.08	13.4	1.7	O
II	CH ₃ I	0.87	0.03	0.65	0.15	C
III	CH ₃ I	0.99	0.02	1.88	0.46	C

^a I = CH₃COCH₂COCH₃; II = CH₃COCHCOCH₃; III = C₆H₅COCH₂COCH₃.



of buffer capacity in the pH range 5–9 demonstrated that it was free from tributylammonium hydrogen sulfate.

The kinetic measurements were performed in the following way. 25 ml of a solution of the compound HA in methylene chloride was added to 25 ml of an aqueous solution containing tetrabutylammonium sulphate Q₄SO₄ and Na₂SO₄ to give an ionic strength corresponding to 0.5 M Na₂SO₄. The flask with this mixture was placed in a water thermostat at 25.0 °C and fitted with a very efficient Teflon stirrer that vigorously mixed the two layers. A glass and a calomel electrode, as well as a capillary tube for the addition of aqueous NaOH from a syringe, were introduced and connected to an instrument (Radiometer Titrator TT11 with Titrigraph SBR2/SBU2) which registers the quantity of NaOH needed to keep the pH constant. A pH value and a proper paper speed were chosen and the experiment started. When equilibrium was reached, 1.000 ml of methyl iodide, or dimethyl sulfate, was rapidly injected. The reaction was followed by registering the volume L' of NaOH added to keep the pH constant.

The distribution measurements were performed with the same type of equipment, but the instrument was now used as a pH meter. Portions of sodium hydroxide corresponding to about 10 % of the total quantity of HA present were introduced and the pH was measured after each addition. When Q⁺ was present, it was usually not necessary to stop the stirrer in order to get a stable reading, in the other cases, the layers were allowed to separate and the pH was read in the aqueous layer.

Methylacetylacetone was prepared by the method of Brändström,⁶ comp. Ref. 7. Acetylacetone was removed from the product by dissolving it in 10 parts of ether and extracting it with small portions of 1 M sodium hydroxide, each corresponding to about 5 % of the total content of diketone. The pH of each aqueous extract was measured. The extraction was continued until the acetyl-

acetone content could be calculated to be about 0.1 %. The apparent dissociation constants of acetylacetone and methylacetone are 9.6 and 11.6, respectively, in this two layer system. (The pH of the two last portions were 11.5 and 11.7, respectively).

The isopropylation of the tetrabutylammonium acetylacetonate was performed in methylene chloride by the method of Brändström and Junggren.⁸

Acknowledgement. This work has been made possible by a one year guest professorship at Kemisk Institut, Århus, Denmark. The author is also indebted to Dr. Bo Svensmark-Jensen who prepared the data programs used in the calculations.

REFERENCES

- Brändström, A. *Ark. Kemi* 6 (1953) 155.
- Kurts, A. L., Genkina, N. K., Macias, A., Beletskaya, I. P. and Reutov, O. A. *Tetrahedron* 27 (1971) 4777.
- Brändström, A. and Junggren, U. *Acta Chem. Scand.* 23 (1969) 2204.
- Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, Wiley-Interscience, New York 1972, p. 14.
- Marshall, H. P. and Grunwald, E. *J. Chem. Phys.* 21 (1953) 2143.
- Brändström, A. *Ark. Kemi* 2 (1950) 596.
- Johnson, A. W., Markham, E. and Price, R. *Org. Synth. Coll. Vol.* V (1973) 785.
- Brändström, A. and Junggren, U. *Acta Chem. Scand.* 25 (1971) 1469.
- Brändström, A. *Ark. Kemi* 7 (1954) 81.
- Brändström, A. *Preparative Ion Pair Extraction*, Apotekarsocieteten, Box 1136, S-111 81 Stockholm 1974, p. 104.
- Schill, G. In Marinsky, J. A. and Marcus, Y., Eds., *Ion Exchange and Solvent Extraction*, Marcel Dekker, New York 1974, Vol. 6, pp. 1–57.

Received June 25, 1975.