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Solvent and Leaving Group Effects on the Mono- vs. Dialkylation of Alkali Salts of Diethyl Malonate with 1,2-bis-, 1,2,4,5-tetrakis- and 1,2,3,4,5,6-hexakis-(Halomethyl)benzenes. A New Insight into Selectivity Control of Malonester Synthesis.

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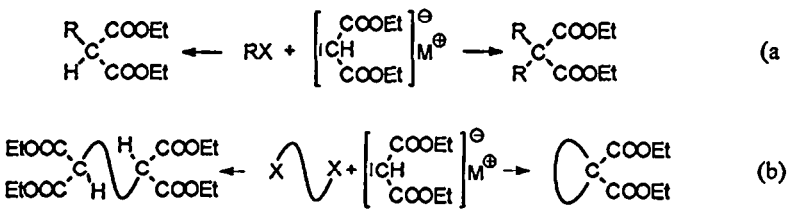
Abstract: Contrary to the widely held opinion that protic ("acidic") solvents favor monoalkylation whereas aprotic ("inert") solvents support dialkylation of diethyl malonate carbanion, exactly opposite results have been obtained in the reaction of the dibromide **7**, tetrabromide **4** and hexabromide **1** in ethanol and dimethyl sulfoxide, the former solvent preferring strongly dialkylation (cyclization) and the latter monoalkylation. Investigation in a broader spectrum of solvents demonstrated that hydrogen bonding as well as ion-pairing may play an important role in the selectivity control, both strongly supporting dialkylation. When a separation of ion-pairs is induced with 18-crown-6, monoalkylation prevails in the reaction. The solvent and the leaving group employed have been found to participate in the selectivity control. In DMSO, propensity to dialkylation increases strongly in the order I < Br << Cl , again in discord with earlier predictions. Rationale for the novel findings is provided on the basis of kinetic analysis of the overall reaction and is expressed by the limiting equations (5) and (7).· © 1997 Elsevier Science Ltd.

INTRODUCTION

Solvents have been shown to play an important role in the selectivity control of numerous carbanion reactions.[1] In malonester alkylation, somewhat surprisingly, the intriguing problem has received only a sparse attention so far,[2-4] the available evidence being based, in most instances, on incomplete and not always reliable data.

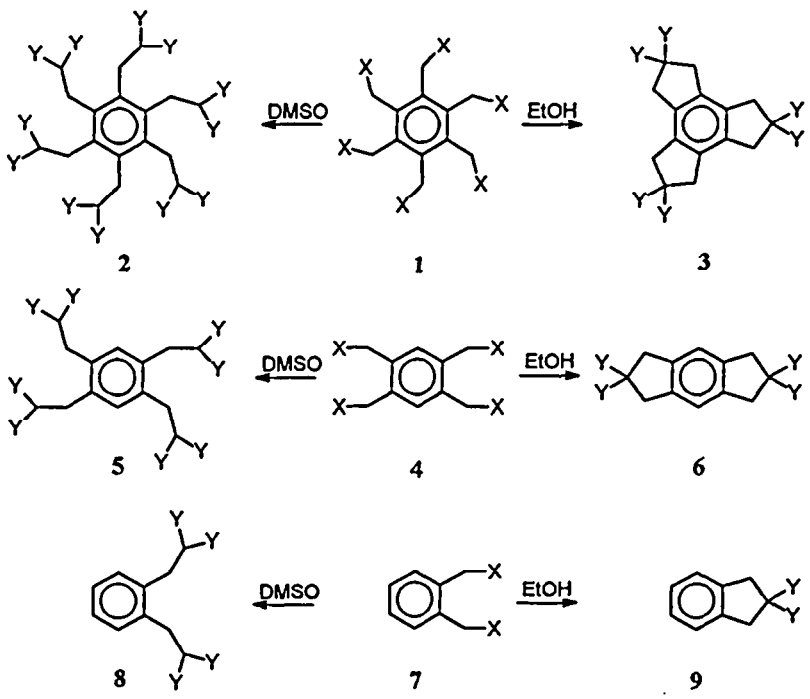
In this widely exploited reaction, the pertinent problem of selectivity concerns mono- vs. dialkylation of the malonester carbanion (Scheme 1a). When an α,ω-dihalide or disulphonate takes part in the alkylation, the selectivity control implies at the same time the duality of acyclic vs. cyclic product formation (Scheme 1b).



Scheme 1

RESULTS AND DISCUSSION

As part of our interest in multiarmed compounds and dendrimer synthesis, we have investigated reaction of the easily accessible[5] hexakis(bromomethyl)benzene **1** (X=Br) with the sodium salt of diethyl malonate. Unexpectedly, different products have been found to arise in the reaction performed in DMSO and ethanol. The monocyclic product of a hexafold monoalkylation **2** prevailed greatly in DMSO, whereas the tetracyclic product of a threefold dialkylation **3** was obtained in ethanol. A quite analogous situation arose in the reaction of the homologous 1,2,4,5-tetrakis- and 1,2-bis(bromomethyl)benzene **4** (X=Br) and **7** (X=Br) (Scheme 2).



2 **1** **3**

5 **4** **6**

8 **7** **9**

1 - 9 : X = Br, Y = COOEt

Scheme 2

Table 1. Effect of Solvent on Product Distribution in the Alkylation of Sodium Salt of Diethyl Malonate with Bromides **1**, **4** and **7** (X=Br).

Bromide	Solvent	Stoichiometry[a]	Product Composition[c] (mol%)	Selectivity[d]
1	DMSO	1	**2** (77.9); **3** (1.4); **10** (17.5); **11** (2.6); **12** (0.6)	56 : 1
1	EtOH	1	**2** (3.3); **3** (18.5); **11** (63.8); **12** (14.4)	1 : 5.6
1	EtOH	0.5[b]	**2** (1.2); **3** (93.4); **11** (3.8); **12** (1.6)	1 : 78
4	DMSO	1	**5** (78.8); **6** (2.2); **13** (19.0)	36 : 1
4	EtOH	1	**5** (3.0); **6**(68.1); **13** (28.9)	1 : 23
4	EtOH	0.5[b]	**5** (1.5); **6** (97.0); **13** (1.5)	1 : 65
7	DMSO	1	**8** (96.0); **9** (4.0)	24 : 1
7	EtOH	1	**8** (16.8); **9** (83.2)	1 : 5
7	EtOH	0.5[b]	**8** (1.3); **9** (98.7)	1 : 76

[a] Number of equivalents of sodium salt of diethyl malonate per one -CH_2Br unit. The starting concentration of the bromide was 5.10^{-2} mol.dm^{-3}.

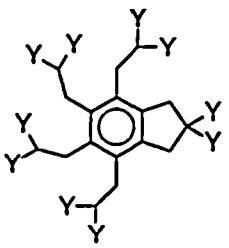
[b] External base (0.5 eq. of EtONa per one -CH_2Br unit) was also present in the reaction mixture.

[c] After heating at 50 °C for 5 h.

[d] Exclusive monoalkylation/exclusive dialkylation ratio according to Scheme 2: **2**/**3** from **1**; **5**/**6** from **4**; **8**/**9** from **7**.

"Hybrid" Alkylation By-products and their Suppression

HPLC analysis of the individual reactions (Table 1) quantifies the divergent selectivities outlined in Scheme 2. At the same time, the analysis reveals occurrence of the "hybrid" by-products arising from a mixed mono- and dialkylation of the starting malonate salt (**1** → **10**,**11**,**12**; **4** → **13**). Under uniform stoichiometric conditions (one equivalent of sodium malonate per one -CH_2Br unit), the proportion of the by-products is much greater in ethanol than in DMSO. Upon a fine tuning of the stoichiometry in ethanol, in favor of dialkylation (*vide infra*), the by-products can be suppressed very substantially and the dialkylation selectivity can be increased markedly.



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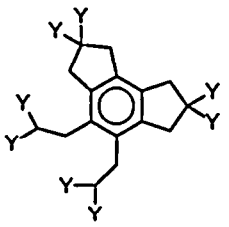

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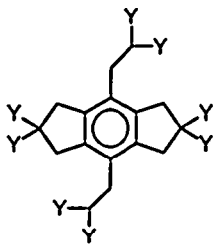

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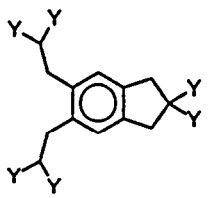

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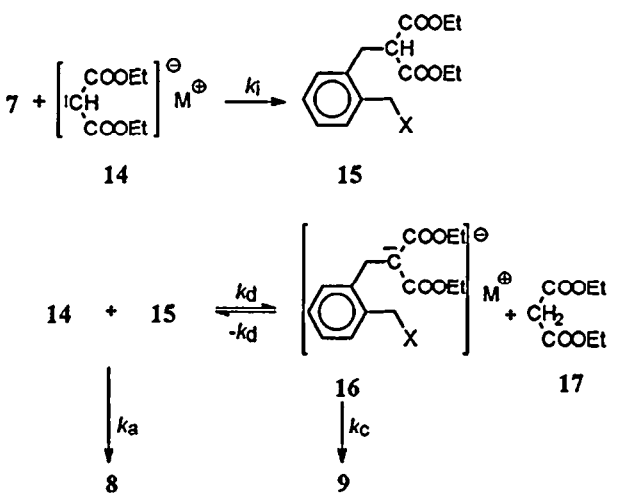
10 - 13 : Y = COOEt

Kinetic Analysis of the Model Alkylation Reaction

In order to analyze the solvent effect in Table 1, we have chosen the alkylation of the alkali salt of diethyl malonate **14** with the dihalide **7** as a model reaction. Scheme 3 summarizes the sequence of reaction steps anticipated[6] in the alkylation.



Scheme 3

In the first step, the dihalide **7** reacts with the malonate salt **14** under formation of the intermediate **15**. A further molecule of the carbanion **14** attacks the C-X bond of the intermediate **15** yielding the bis-monoalkylated product **8**. Alternatively, the proton transfer from **15** to **14** leads to the carbanion **16** which cyclises subsequently under formation of the dialkylated product **9**.

A closer consideration of Scheme 3 suggests that two limiting, kinetically distinct, situations may arise[7] in the alkylation, depending on the relative rates of the carbanion **16** formation and its cyclization.

If, in one extreme, the proton transfer from **15** to **14** is *faster* than the subsequent cyclization of the resulting carbanion **16** ($k_d >> k_c$), the rates of bis-monoalkylation and dialkylation, v_a and v_c respectively, are given by the equations

$$v_a = k_a[14][15] \tag{1}$$

and

$$v_c = k_c[16] \tag{2}$$

so that for the alkylation selectivity holds

$$v_a/v_c = k_a[14][15]/{}_c[16] \tag{3}$$

Taking into account the acidobasic equilibrium[9] between the non-alkylated and haloalkylated malonate species,[10] **14** + **15** $\rightleftharpoons$ **16** + **17**, and the corresponding equilibrium constant K_1

$$K_1 = [16][17]/[14][15] \tag{4}$$

the equation (3) can be rewritten as

$$v_a/v_c = k_a[17]/k_cK_1 \tag{5}$$

If, in the other extreme, the proton transfer from **15** to **14** is *slower* than the subsequent cyclization of **16** ($k_d << k_c$), the rate of dialkylation is expressed by

$$v_c = k_d[14][15] \tag{6}$$

and together with eq. (1) it gives for the alkylation selectivity

$$v_a/v_c = k_a/k_d \tag{7}$$

In order to probe whether the limiting equations (5) and (7) may account for the divergent alkylation selectivity observed in DMSO and ethanol, two subsidiary experiments have been performed aiming to assess the relative rates of the individual pathways in Scheme 3.

Stepwise Addition of Diethyl Malonate Carbanion 14 to the Solution of Dibromide 7 (X=Br)

Two equivalents of the sodium salt **14** (M^+=Na^+) were added stepwise, in four aliquot portions, to the solution of the dibromide **7** (X=Br) in DMSO or ethanol. GLC analysis of the individual samples withdrawn from the reaction mixture following consumption of each added portion of **14** showed (Table 2) a fundamental difference between the two solvents concerning the relative rates of the consecutive pathways leading to the cyclic product **9**. In DMSO, the formation of **15** is much faster than its subsequent conversion into the cyclic product **9**, whereas the opposite is true in ethanol. The relative rates of the consecutive pathways leading to the acyclic product **8** are distinctly less different.

Table 2. Formation and Subsequent Transformation of Intermediate **15** Induced upon Gradual Addition of Sodium Salt **14** (M^+=Na^+) to Dibromide **7** (X=Br) Dissolved in DMSO and EtOH.

Solvent	Equivalents of 14[a]	Composition[b] (in %)			
		7	**15**	**8**	**9**
DMSO	0.5	58.5	33.2	6.3	2.0
	1.0	29.9	38.5	28.7	2.9
	1.5	8.7	26.6	58.2	6.5
	2.0	2.6	1.6	88.0	7.8
EtOH	0.5	79.8	0.2	0.5	19.5
	1.0	45.8	0.9	1.3	51.9
	1.5	22.8	0.6	2.5	74.1
	2.0	0.2	0.2	5.4	94.2

[a] Two equivalents of **14** were added to a solution of **7** (1.10^{-1} mol.dm^{-3}) in four aliquot portions. After addition of each portion, the mixture was heated at 50°C for 0.5 h and then analyzed.

[b] GLC had to be used for separation of the complicated reaction mixture, providing less accurate data than HPLC analysis employed in Tables 1, 3, 4, 5.

Effect of Free Diethyl Malonate 17

As it follows from the kinetic analysis of Scheme 3, the value of the mono- vs. dialkylated product ratio **8**/**9** depends on the concentration of the free diethyl malonate **17** if, and only if, $k_d > k_c$ (cf. eq. (5) vs. eq. (7)). Examination of the effect of [**17**] on the **8**/**9** ratio may thus distinguish between the extreme situations $k_d > k_c$ and $k_d < k_c$ in the alkylation. The pertinent results concerning the reaction of the malonate salt **14** (M^+=Na^+) with the dibromide **7** (X=Br) in the two investigated solvents are summarized in Table 3.

Table 3. Effect of Free Diethyl Malonate **17** on Product Distribution in the Alkylation of Sodium Salt **14** ($M^+=Na^+$) with Dibromide **7** (X=Br) in DMSO and EtOH.

Solvent	17 : 14 Ratio[a]	8 (%)	9 (%)	8 / 9
DMSO	0 : 1	96	4	24 (0.4)[b]
	2.5 : 1	98	2	49 (0.7)[b]
	5 : 1	98	2	49 (1.1)[b]
	10 : 1	98	2	49 (1.7)[b]
EtOH	0 : 1	27	73	0.4
	2.5 : 1	64	36	1.8
	5 : 1	82	18	4.6
	10 : 1	89	11	8.1

[a] The ratios 17:14 were calculated[11] from the analytical concentrations of diethyl malonate and the external base (NaH in DMSO ; NaOEt in EtOH) employed in the individual runs. The ratios 14 : 7 were kept constant (2:1) in the Table; the starting concentration of 7 was 1.10^{-1} mol.dm^{-3}. Heated at 50°C for 2 h.

[b] Data for the corresponding reaction of the dichloride 7 (X=Cl).

A very pronounced dependence of the ratio 8/9 on the concentration of the free diethyl malonate **17** has been found in the reaction of the dibromide 7 (X=Br) in ethanol, indicating that $k_d > k_c$. In contrast, a near-independence of the ratio 8/9 on [17] is apparent in the corresponding reaction of the dibromide 7 (X=Br) performed in DMSO, demonstrating that $k_d < k_c$.

In this way, it follows that the selectivity in ethanol is determined by eq. (5), in which the intrinsic propensity of the system to cyclization (expressed by k_c) provides the driving force for the preferential dialkylation. In dimethyl sulfoxide, on the other hand, the selectivity is determined by eq. (7), in which this particular factor is absent and the rate of dialkylation is limited by the preceding proton-transfer step (k_d).

Alkylation Selectivity in a Broader Spectrum of Solvents. Effect of Ion Pairing and Hydrogen Bonding.

In order to assess which specific properties of solvent may account for the selectivity control, we have investigated alkylation of the potassium (more soluble) salt of diethyl malonate **14** ($M^+=K^+$) with the dibromide **7** (X=Br) in a broader spectrum of solvents. As Table 4 shows, selectivity of the alkylation depends strongly on the solvent polarity, as evidenced by a qualitative correlation between the value of 8/9 ratio and the dielectric constant of

the solvent employed in the reaction. The bis-monoalkylation leading to **8** prevails in the most polar solvent, DMSO, whereas the dialkylation leading to **9** dominates in the least polar one, benzene.

The ion pairing capability of solvent plays a very essential role in this relationship, as evidenced by the suppression of the dialkylation pathway in solvents of low polarity upon the addition of 18-crown-6-ether (Table 4).

Table 4. Effect of Solvent Polarity (ε) and 18-Crown-6 on Product Distribution in the Alkylation of Potassium Salt **14** (M^+=K^+) with Dibromide **7** (X=Br)

Solvent (ε)	14 : (18-crown-6)[a]	8 (%)	9 (%)
benzene (2.3)	1 : 0	8	92
	1 : 1	91	8
THF (7.3)	1 : 0	29	71
	1 : 1	73	27
t-BuOH (12.20)	1 : 0	23	77
	1 : 1	85	15
EtOH (24.55)	1 : 0	27	73
	1 : 1	19	81
CH_3CN (37.5)	1 : 0	41	59
	1 : 1	54	46
DMSO (53.10)	1 : 0	90	10
	1 : 1	94	6

[a] The molar ratio 14 : 7 was kept constant (2 : 1) in the Table. The starting concentration of 7 was 1.10^{-1} mol.dm^{-3}. Heated at 50 °C for 2 h.

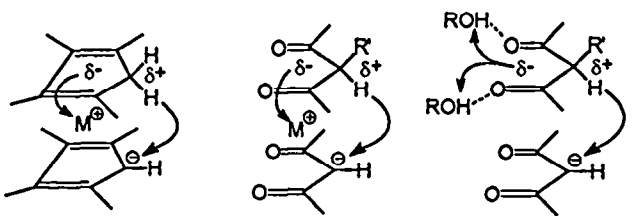
It may be inferred accordingly that ion pairing supports the dialkylation, whereas separation of ion pairs promotes the bis-monoalkylation reaction. A plausible rationale for this conclusion can be provided if a differential rate effect of ion pairing on the S_N2 displacement vs. the proton transfer step in the investigated reaction is taken into account.

According to ample literature evidence,[1] a pronounced slowing-down of S_N2 displacements involving a metal salt as nucleophile is observed usually under ion pairing conditions. In contrast, numerous precedents exist in the literature[13,14] showing that contact ion-paired species may be more reactive than the separated ions in proton-transfer reactions. As a pertinent example, Hogen-Esch and Smid observed[14] that the contact ion-paired species reacted faster than the solvent-separated ion-pair or free carbanion in the proton transfer between fluorene and a fluorenyl

carbanion. A simple model of the activating effect of the metal counterion was suggested (Scheme 4a) as an explanation, which can be easily applied to the proton-transfer step, k_d, also in the present reaction (Scheme 4b).

In terms of the above kinetic analysis of the malonester alkylation, such a promotion of the proton-transfer step, k_d, over the intramolecular S_N2 displacement, k_c, may induce a reversal[15] of the inequity $k_d < k_c$ into $k_d > k_c$. *The effect of ion-pairing can be thus interpreted in terms of the kinetic dichotomy given by the limiting equations (5) and (7).*

Conceivably, hydrogen bonding may exert a similar activating effect (Scheme 4c) as the metal ion pairing (Scheme 4b) on the rate of the proton-transfer, k_d, in the reaction . This can explain the striking difference in the alkylation selectivity which has been observed between two polar (ion-pairs separating) solvents, the protic ethanol and the aprotic dimethyl sulphoxide, in the absence as well as in the presence of 18-crown-6-ether (Table 4).



Scheme 4

Effect of Leaving Group.

Table 5 summarizes the ratios, in which the product of bis-monoalkylation **8** and the product of dialkylation **9** arise in the reaction of three different dihalides **7** (X= I, Br, Cl) with the sodium salt **14** (M^+=Na^+) in DMSO and ethanol. In DMSO, the value of the **8/9** ratio decreases dramatically along the dihalide series following the order I > Br >> Cl . In ethanol, on the other hand, only minor changes of the **8/9** ratio occur in the series.

It is known that rates of S_N2 displacement from alkyl halides depend strongly on the leaving group, decreasing in the order I ($\sim 10^3$) > Br ($\sim 10^2$) >> Cl (~1). A similar decrease of the rate of the intramolecular displacement (k_c) can also be assumed in the dihalide series **7**. This may induce a reversal of the inequity $k_d < k_c$ into $k_d > k_c$ on the transition from the most reactive (X=I) to the least reactive (X=Cl) dihalide, accounting for the striking leaving group effect on selectivity observed in DMSO. The pronounced dependence of the ratio **8/9** on **[17]** found for the reaction of the dichloride **7** (X=Cl) in DMSO (Table 3, data in parentheses), in a contrast to the dibromide **7** (X=Br), lends full support to this suggestion.

Table 5. Effect of Leaving Group X on Product Distribution in the Reaction of Sodium Salt **14** (M^+=Na^+) with the three Dihalides **7** (X = I, Br, Cl) in DMSO and EtOH.

X[a]	DMSO		EtOH	
	8 (%)	**9** (%)	**8** (%)	**9** (%)
I	99	1	33	67
Br	97	3	34	66
Cl	27	73	26	74

[a] The molar ratio **14** : **7** was kept constant (2:1) in the Table; the starting concentration of **7** was 1.10^{-1} mol.dm^{-3}. Heated at 50 °C for 2 h.

As a corollary, it follows that the leaving group effect can also be interpreted in terms of the kinetic dichotomy in Scheme 3. In DMSO, the two more reactive dihalides **7** (X=I and X=Br) react with the malonate carbanion obeying eq. (7), whereas the most sluggish dichloride (**7**; X=Cl) reacts in accord with eq. (5). In ethanol, the situation is different, since all three investigated dihalides obey eq. (5). This may explain why the leaving group effect on the alkylation selectivity is much stronger in the former than in the latter solvent.

Concluding Remarks Concerning the Alkylation Selectivity

Interpretation of the selectivity in kinetically controlled reactions is relatively simple when the rate- (product-) determining steps in the competing processes do not change with reaction variables. In such customary situations, a straightforward explanation of selectivity can be given in terms of the differential effect which exerts a given reaction variable upon the individual processes.

In the present case, however, the situation is different, and in discussion of selectivity possibly unprecedental, since the rate- (product-) determining step varies with reaction variables, as it was demonstrated in Table 3 by the solvent (DMSO vs. EtOH) as well as leaving group (**7**; X=Br vs. **7**; X=Cl in DMSO) effects. Identification of the rate- (product-) determining step *via* kinetic analysis thus appeared to be a necessary prerequisite for a meaningful interpretation of the observed pattern of selectivity.

SUMMARY

Contrary to the widely circulated but never satisfactorily documented opinion[2-4] that protic ("acidic") solvents favor monoalkylation whereas aprotic ("inert") solvents support dialkylation of diethyl malonate carbanion **14**, exactly opposite results have been obtained in the reaction of the dibromide **7**, tetrabromide **4** and hexabromide **1** in ethanol and dimethyl sulfoxide, the former solvent preferring strongly dialkylation and the latter monoalkylation of **14**. Examination of the individual pathways participating in the model alkylation of **14** with **7** (Scheme 3) showed that the sequence of reaction steps leading to the dialkylated cyclic product **9** is responsible for the observed solvent effect. In ethanol, the proton transfer pathway **15** → **16** is faster than the subsequent cyclization **16** → **9**, whereas in dimethyl sulfoxide the opposite is true. As a consequence, selectivity in ethanol is determined by eq. (5), in which the intrinsic propensity of the system to cyclization (expressed by k_c) provides the driving force for the preferential dialkylation. In dimethyl sulfoxide, on the other hand, selectivity is determined by eq. (7), in which this crucial factor is absent and the dialkylation is limited by the preceding proton-transfer step (k_d).

Investigation in a broader spectrum of solvents differing in polarity demonstrated that hydrogen bonding as well as ion-pairing play an important role in the selectivity control, both strongly supporting the dialkylation. When a separation of ion pairs is induced (in aprotic solvents) with 18-crown-6, the monoalkylation prevails in the reaction.

Together with the solvent, the leaving group also participates in the selectivity control of the investigated alkylation. It has been found, in DMSO, that the propensity to dialkylation gradually increases in the dihalide **7** series on going from the most reactive iodide (X=I) to the least reactive chloride (X=Cl) leaving group, which is also in discord with earlier predictions.[2-4]

Presumably, other factors than solvent and leaving group may also take part in the selectivity control of the alkylation. It will be shown in the forthcoming paper[16] that alkyl structure of both reaction partners (dihalide and carbanion) plays an essential role.

EXPERIMENTAL SECTION

General

All solvents employed in the reactivity study were dried by storing over molecular sieves. Melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra (200 MHz, FT mode) were recorded in $CDCl_3$ with TMS as the internal standard. EI mass spectra were obtained at 70 eV; FAB spectra were measured in 2-hydroxyethyl sulfide matrix in $CHCl_3$ as solvent. GLC analyses were performed on a HP-1 column (methylsilicone, 5 m × 0.53 mm × 2.65 nm), temperature gradient from 50 to 300 °C, flame ionization detector. HPLC analyses were

carried out on silica gel (column Partisil 10 Silica 250 × 4.6 mm, Pye Unicam), light petroleum - 2-propanol (99.5 : 0.5 - 97.0 : 3.0) gradient, UV detector (230 nm). Quantitative evaluation of chromatograms was made using an internal standard. Preparative HPLC was carried out on a 250 × 50 mm silica gel column in light petroleum - - 2-propanol (99:1 - 90:10).

Hexaethyl 1,2,3,4,5,6-Benzenehexa(α-ethoxycarbonylpropanoate) **2**

Sodium hydride (60% in mineral oil, 5.6 g, 140 mmol) was washed with light petroleum and suspended in dimethyl sulfoxide (200 mL). Diethyl malonate (28.8 g, 180 mmol) was added dropwise under cooling to the stirred slurry, followed by hexabromide **1** (12.73 g, 20 mmol). The reaction mixture was heated at 80 °C for 2 h, poured into water (1000 mL), neutralized with 0.1 M aqueous HCl and extracted with ether (4×200 mL). The combined extracts were washed with water (200 mL), dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was crystallized from heptane yielding 18.55 g (83%) of **2**, mp 158-162 °C, after recrystallization from ethanol mp 168-170 °C. ^{1}H NMR δ 1.23 (t, 36H, J = 7.0 Hz), 3.25-3.50 (m, 18H), 4.0-4.3 (m, 24H); FAB MS *m/z* (relative intensity) 1112 (MH^+, 100), 952 (35), 905 (15), 846(35), 773 (15), 673 (25), 613 (25). Anal. Calcd. for $C_{54}H_{78}O_{24}$ (1111.16) C, 58.34; H, 7.08; Found C, 57.95; H, 7.03.

Hexaethyl 2,2,5,5,8,8-Trindanehexacarboxylate[17] **3**

Sodium (1.61 g, 70 mmol) was dissolved in absolute ethanol (100 mL) and diethyl malonate (5.29 g, 33 mmol) in ethanol (25 mL) was added dropwise to the solution. After addition of the hexabromide **1** (6.36 g, 10 mmol), the reaction mixture was heated under reflux for 5 h and the solvent was evaporated *in vacuo*. The residue was mixed with water (50 mL), neutralized with 1 M HCl and extracted with chloroform (4×50 mL). The combined extracts were dried over $MgSO_4$, evaporated and the residue was crystallized from ethyl acetate. Yield 4.04 g (64%), mp 185-186 °C. ^{1}H NMR δ 1.26 (t, 18H, J = 6 Hz), 3.46 (s, 12H), 4.20 (q, 12H, J = 6 Hz); FAB MS *m/z* (relative intensity) 632 (MH^+, 100), 604 (40), 558 (90), 483 (30). Anal. Calcd. for $C_{33}H_{42}O_{12}$ (630.68) C, 62.84; H, 6.71; Found C, 62.42; H, 6.80.

Tetraethyl 1,2,4,5-Benzenetetra(α-ethoxycarbonylpropanoate) **5**

Sodium hydride (60% in mineral oil, 0.88 g, 22 mmol) was washed with light petroleum and suspended in dimethyl sulfoxide (25 mL). The solution of diethyl malonate (5.29 g, 33 mmol) in dimethyl sulfoxide (25 mL) was slowly added to the stirred slurry, followed by tetrabromide **4** (2.25 g, 5 mmol) dissolved in 25 mL dimethyl sulfoxide. After stirring for 30 min at rt, the reaction mixture was poured into water (200 mL), neutralized with 0.1 M aqueous HCl and extracted with ether (4×40 mL). The combined extracts were washed with water (2×20 mL), dried over $MgSO_4$ and the solvent was evaporated. The unreacted diethyl malonate was distilled off (100 °C/50 Pa,

Kugelrohr) and the residue was crystallized from ether-light petroleum. Yield 2.91 g (76%), mp 58-60 °C. ^{1}H NMR δ 1.21 (t, 24H, J = 7.2 Hz), 3.19 (d, 8H, J = 7.5 Hz), 3.61 (t, 4H, J = 7.5 Hz), 4.14 (q, 16H, J = 7.2 Hz), 6.93 (s, 2H); EI MS *m/z* (relative intensity) 766 (M^+, 35), 674 (40), 628 (50), 514 (40), 29 (100). Anal. Calcd. for $C_{38}H_{54}O_{16}$ (766.83) C, 59.51; H, 7.10; Found C, 59.54; H, 7.11.

Tetraethyl 1,2,3,5,6,7-Hexahydro-s-indacene-2,2,6,6-tetracarboxylate **6**

Sodium (1.38 g, 60 mmol) was dissolved in absolute ethanol (75 mL), diethyl malonate (4.81 g, 30 mmol) was added slowly to the stirred solution, followed by tetrabromide **4** (4.50 g, 10 mmol). The reaction mixture was heated under reflux for 4 h and the solvent was evaporated. The residue was partitioned between ether (50 mL) and water (50 mL) and neutralized with 1 M HCl. The organic layer was separated and the aqueous phase was extracted with ether (3×30 mL). The combined extracts were dried over $MgSO_4$, the solvent was evaporated and the residue was crystallized from ether - light petroleum. Yield 3.62 g (81%), mp 160-162 °C. ^{1}H NMR δ 1.25 (t, 12H, J = 7.2 Hz), 3.51 (s, 8H), 4.19 (q, 8H, 7.2 Hz), 7.00 (s, 2H); EI MS *m/z* (relative intensity) 466 (M^+, 30), 401 (5), 372 (35), 298 (50), 153 (20), 100 (20), 71 (60), 57 (60), 43 (100). Anal. Calcd. for $C_{24}H_{30}O_8$ (446.50) C, 64.55; H, 6.77; Found C, 64.53; H, 6.74.

Diethyl 1,2-Benzenedi(α-ethoxycarbonylpropanoate) **8**

Sodium hydride (60% in mineral oil, 2.0 g, 50 mmol) was washed with light petroleum and suspended in dimethyl sulfoxide (25 mL). A solution of diethyl malonate (8.0 g, 50 mmol) in dimethyl sulfoxide (25 mL) was slowly added to the stirred slurry, followed by dibromide **7** (5.28 g, 20 mmol) dissolved in dimethyl sulfoxide (25 mL). The reaction mixture was stirred at rt for 30 min and worked up as described for **5**. Distillation at 170-200 °C/15 Pa (Kugelrohr) afforded the product as an oil (7.05 g, 83%). ^{1}H NMR δ 1.20 (t, 12H, J = 7.1 Hz), 3.28 (d, 4H, J = 7.6 Hz), 3.70 (t, 2H, J = 7.6 Hz), 4.15 (q, 8H, 7.1 Hz), 7.12 (m, 4H); EI MS *m/z* (relative intensity) 422 (M^+, 60), 377 (45), 284 (100), 216 (50), 211 (50), 210 (80), 189 (45), 117 (60). Anal. Calcd. for $C_{22}H_{30}O_8$ (422.48) C, 62.54; H, 7.16; Found C, 62.11; H, 7.03.

Diethyl 2,2-Indanedicarboxylate **9**

Sodium (0.51 g, 22 mmol) was dissolved in absolute ethanol (10 mL) and diethyl malonate (1.76 g, 11 mmol) in ethanol (5 mL) was slowly added to the stirred solution, followed by dibromide **7** (2.64 g, 10 mmol). After heating under reflux for 3 h and an usual work-up, the product was obtained by distillation (140-150 °C/20 Pa, Kugelrohr) as an oil (1.95 g, 74%) which solidified on standing, mp 36-37 °C, lit.[18] 38 °C. Spectral data (^{1}H-MNR, MS) were in accord with those in lit.[19].

Tetraethyl 2,2-Di(ethoxycarbonyl)-4,5,6,7-indanetetra(α-ethoxycarbonylpropanoate) **10**

Isolated from the mother liquors after crystallization of **2**. Preparative HPLC afforded an oil which crystallized on standing in refrigerator, mp 48-52 °C. ^{1}H NMR δ 1.1-1.3 (m, 30H), 3.2-3.8 (m, 16H), 4.05-4.20 (m, 20H); FAB MS *m/z* (relative intensity) 951 (MH^+, 10), 905 (15), 791 (25), 597 (15), 127 (100); HRMS(FAB) Found 951.3905 (MH^+), $C_{47}H_{67}O_{20}$ requires 951.4227.

*Diethyl 2,2,7,7-Tetra(ethoxycarbonyl)-1,2,3,6,7,8-hexahydro-*as*-4,5-indacenedi(α-ethoxycarbonylpropanoate)* **11**

Isolated from the mother liquors after crystallization of **3**. A repeated HPLC afforded an oil which solidified on standing in refrigerator, mp 85-87 °C after recrystallization from dioxane-light petroleum. ^{1}H NMR δ 1.17 (t, 12H, J = 7 Hz), 1.26 (t, 12H, J = 7 Hz), 3.26 (d, 4H, J = 8 Hz), 3.44 (s, 4H), 3.51 (s, 4H), 3.56 (t, 2H, J = 8 Hz), 4.05-4.25 (m, 16H); FAB MS *m/z* (relative intensity) 791 (MH^+, 20), 631 (65), 557 (45), 399 (55), 325 (95), 253 (60), 191 (85), 127 (100); HRMS(FAB) Found 791.3196 (MH^+), $C_{40}H_{55}O_{16}$ requires 791.3490. Anal. Calcd. for $C_{40}H_{54}O_{16}$ (790.83) C, 60.75; H, 6.88; Found C, 60.84; H, 6.63.

*Diethyl 2,2,6,6-Tetra(ethoxycarbonyl)-1,2,3,5,6,7-hexahydro-*s*-4,8-indacenedi(α-ethoxycarbonylpropanoate)* **12**

Isolated, simultaneously with **11**, by a repeated HPLC of the mother liquors from crystallization of **3**. Solidified on standing, mp 92-94 °C (dioxane - light petroleum). ^{1}H NMR δ 1.17 (t, 12H, J = 7 Hz), 1.26 (t, 12H, J = 7 Hz), 3.13 (d, 4H, J = 8 Hz), 3.50 (s, 8H), 3.62 (t, 2H, J = 8 Hz), 4.05-4.25 (m, 16H); FAB MS *m/z* (relative intensity) 791 (MH^+, 40), 717 (55), 671 (50), 631 (100), 557 (90), 483 (65), 411 (70); HRMS(FAB) Found 791.3172 (MH^+), $C_{40}H_{55}O_{16}$ requires 791.3490.

Diethyl 2,2-Di(ethoxycarbonyl)-5,6-indanedi(α-ethoxycarbonylpropanoate) **13**

Isolated from the mother liquors after crystallization of **5**. Preparative HPLC afforded an oil which solidified on standing in refrigerator, mp 80-82 °C (ether - light petroleum). ^{1}H NMR δ 1.1-1.3 (m, 18H), 3.22 (d, 4H, J = 7.6 Hz), 3.48 (s, 4H), 3.64 (t, 2H, J = 7.6 Hz), 4.09-4.24 (m, 12H), 6.98 (s, 2H); EI MS *m/z* (relative intensity) 606 (M^+, 15), 532 (15), 501 (20), 446 (35), 153 (20), 57 (25), 44 (30), 29 (100); HRMS(EI) Found 606.2685 (M^+), $C_{31}H_{42}O_{12}$ requires 606.2676.

Diethyl (2-Bromomethylphenyl)methylmalonate **15**

Sodium salt of diethyl malonate was prepared on mixing diethyl malonate (2,11 g, 8 mmol) and sodium *tert*-butoxide (0.384 g, 4 mmol) in dimethyl sulfoxide (15 mL). Dibromide **7** was added to the solution, the reaction mixture was stirred at rt for 15 min and worked up in the usual manner. The oily product was isolated by liquid chromatography on silica gel; light petroleum - ether (6:1). ^{1}H NMR δ 1.22 (t, 6H, J = 7.0 Hz), 3.36 (d, 2H, J = 7.6 Hz), 3.78 (t, 1H, J = 7.6 Hz), 4.18 (q, 4H, J = 7.0 Hz), 7.40-7.78 (m, 4H); EI MS *m/z* (relative intensity) 343 (M^+,

46), 298 (34), 263 (100). Anal. Calcd. for $C_{13}H_{19}BrO_4$ (343.22) C, 52.49; H, 5.58; Br, 23.28; Found C, 52.76; H, 5.54; Br, 23.18.

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6. A pre-equilibrium **14** + SH $\rightleftharpoons$ **17** + S^- involving the carbanion **14** and a solvent (SH) has been invoked[2] in earlier discussions of selectivity control and a key role of solvent acidity has been suggested. A solvent of an acidity comparable to that of **17** will reduce concentration of the carbanion **14**. It has been argued accordingly that a large excess of the solvent in the reaction mixture reduces the concentration of the monoalkylated (more basic) carbanion (e.g., **16**) to such a low level that the dialkylation becomes negligible. Thus, monoalkylation has been predicted to prevail in the "acidic" ethanol whereas aprotic ("inert") solvents have been assumed to be more favorable for dialkylation, in a complete disagreement with Table 1.
7. It has been taken for granted in earlier discussions that the malonester deprotonation is faster than the alkylation of the malonester carbanion. Only recently, Mandolini[8] in his brilliant study of the ω-haloalkyl-malonate cyclization noted that it is not always so. No conclusion concerning selectivity control could be drawn, however, from this observation.
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9. Alternative approach employing steady-state approximation for calculation of **[16]** leads to the identical equations (5) and (7) for the extremes $k_d >> k_c$ and $k_d << k_c$, respectively.

10. Accompanying acidobasic equilibria arising from the proton-transfer reaction of **8** with **14** or **16** have been omitted from consideration, in order to make the kinetic analysis tractable. Scheme 3 as well as the proposed equations thus represent a simplification of the actual situation. This simplification, however, does not affect validity of the present discussion. It may be shown that the key equations (5) and (7) become invalid if, and only if, the following two conditions are simultaneously fulfilled : (i) the proportion of **8** in the reaction is high, and (ii) $k_d > k_c$, allowing accumulation of **16** and its fast equilibrium with **8**. Evidence from Table 2 and 3 suggests that only one of the two conditions is fulfilled in DMSO (i) as well as in EtOH (ii).

11. The calculation is based on the tacit assumption that the conversion of the external base into the carbanion **14** proceeds quantitatively. The comparison of pK values of diethyl malonate (16.4 in DMSO, ~17.9 in EtOH) with the corresponding values of the employed solvents (pK_{DMSO} ~35; pK_{EtOH} ~19.1; cf. ref. [12]) justifies such an assumption as a reasonable approximation.

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13. Numerous examples of a proton-transfer acceleration by base ion-pairing have been reported in *syn*-eliminations; see Bartsch, R.A.; Závada, J. *Chem. Rev.* **1980**, *80*, 453-494.

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15. In situation when the promotion of k_d over k_c does not suffice to revert $k_d < k_c$ into $k_d > k_c$, the concurring promotion of k_d over k_a may become operative in the selectivity control, in accordance with eq. (7).

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