Kinetic and Mechanistic Aspects of the Application of Diethyl Malonate as Proton Source during Protonation of Anion Radicals in *N,N*-Dimethylformamide
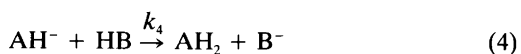
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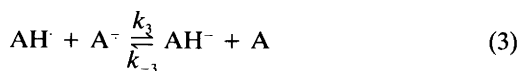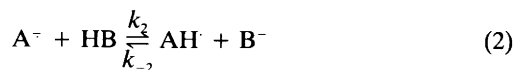
The application of derivative cyclic voltammetry to explore the mechanism of protonation of a number of anion radicals by diethyl malonate in *N,N*-dimethylformamide has demonstrated that the interconversion of the keto and enol forms of the carbon acid plays a dominant role in determining the kinetics. The formation of the enol form, which is the stronger acid, was shown to be effectively catalyzed by addition of base to the solvent system. The catalytic effect of base was strongly diminished in solvent containing water (0.5 M).

The reactions between anion radicals, $A^{\cdot-}$, derived from alternant aromatic hydrocarbons and proton donors, HB, are unique in the sense that the essential steps of the generally accepted mechanism only include the transfer of one electron or one proton (eqns. 1–4). The second electron transfer (eqn. 3) appears in general to be fast and strongly displaced in favor of the right hand side and, accordingly, the first proton transfer step (eqn. 2) becomes irreversible and rate determining.[1–4]

$$A + e^- \rightleftharpoons A^{\cdot-} \tag{1}$$

$$A^{\cdot-} + HB \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} AH^{\cdot} + B^- \tag{2}$$

$$AH^{\cdot} + A^{\cdot-} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} AH^- + A \tag{3}$$

$$AH^- + HB \overset{k_4}{\rightarrow} AH_2 + B^- \tag{4}$$

Mechanistic studies of protonation of anion radicals in aprotic solvents have been made with a large variety of proton sources including water, aliphatic alcohols, phenols and substituted phenols as well as carboxylic acids and carbon acids.[1,2,4–6] In the last group, the attention has been focused almost exclusively on diethyl malonate,[7–19] H_2DEM, the application of which in quantitative work gives rise to complicated rate laws as we will demonstrate.

Results and discussion

During investigations in this laboratory of the kinetic details of protonation of a number of anion radicals including those of phenazine, 2,4,6-triphenylpyrimidine, 1,4-diphenylphthalazine *N*-oxide,[18] naphthalene and a series of substituted naphthalenes, we have observed, contrary to our initial expectations, that the rate of disappearance of $A^{\cdot-}$ in the presence of H_2DEM *increased* upon addition of base. The base, which was made from Bu_4NOH and H_2DEM, was originally believed[18] to be Bu_4N^+, $HDEM^-$. However, the anion of the salt has now been demonstrated to be $EtOOCCH_2COO^-$ (see Experimental) and in the following we will refer to this anion as

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BASE⁻. The accelerating effect is illustrated by the data obtained by derivative cyclic voltammetry,[20] DCV, for the protonation of 2-methoxynaphthalene anion radical in N,N-dimethylformamide, DMF (Table 1). The value of $v_{0.8}$, the sweep rate necessary to keep the derivative peak current ratio equal to 0.8, was observed to be equal to 7.3 V · s⁻¹ for a solution which was 1 mM in substrate and 64 mM in H_2DEM. Addition of increasing amounts of Bu_4N^+, BASE⁻ to the voltammetric solution caused the value of $v_{0.8}$ to increase to more than 50 V · s⁻¹ corresponding to an increase of the apparent protonation rate constant by a factor of 7. A similar effect was observed for the other compounds mentioned above, but the magnitude of the acceleration was found to be dependent on the rate of disappearance of A⁻ in the absence of BASE⁻.

Until now it has been tacitly assumed that the reactions indeed proceed according to the overall stoichiometry given in eqn. (5). However, it has been reported[7] that the reaction between fluorene anion radical, FL⁻, and H_2DEM apparently is not in agreement with eqn. (5), but rather involves reduction of the carbon acid resulting in formation of H_2 and HDEM⁻ and regeneration of FL (eqn. 6). These two reaction schemes can be distinguished by constant current coulometry.[21] Under conditions where $C^0_{H_2DEM}$ is much larger than C^0_A, the stoichiometry of eqn. (5) predicts that 2 F/mol are required for the complete conversion of A to AH_2, whereas eqn. (6), which describes an electrocatalytic reduction of H_2DEM, predicts that the amount of substrate in solution is left unaffected after the passage of this amount of charge. In the actual case, we have found that all the classes of compounds included in the study conform to eqn. (5) within experimental error and we conclude that the reaction accelerated by BASE⁻ is indeed the protonation of A⁻ with no appreciable contributions from other reaction pathways.

Diethyl malonate, owing its acidity to the presence of the two carbonyl groups adjacent to the central methylene unit, is expected to exist in solution in equilibrium with the tautomeric enol form, HDEMH (eqn. 7), like other compounds having the same structural feature.[22-25] As a consequence of this, both the keto form, H_2DEM, and the enol form, HDEMH, can participate in the protonation of A⁻.

$$H_2DEM \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} HDEMH \quad (K_7 = k_7/k_{-7}) \tag{7}$$

$$2\,A^- + 2\,H_2DEM \rightarrow AH_2 + A + 2\,HDEM^- \tag{5}$$

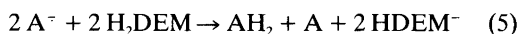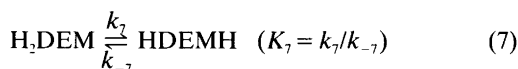$$2\,FL^- + 2\,H_2DEM \rightarrow 2\,FL + H_2 + 2\,HDEM^- \tag{6}$$

Table 1. The effect of addition of BASE⁻ on the rate of disappearance of 2-methoxynaphthalene anion radical in DMF and DMF/H₂O in the presence of H₂DEM.

$C^0_{BASE^-}$/mM	$v^a_{0.8}$/(V · s⁻¹)	$v^b_{0.8}$/(V · s⁻¹)
0	7.3	5.5
1.8	12.9	8.5
3.6	16.1	9.5
6.2	22.0	9.8
10.7	33.1	10.8
17.8	46.4	12.3
26.8	47.8	13.5
40.1	53.1	13.4

C^0_A = 1 mM, $C^0_{H_2DEM}$ = 64 mM, $C^0_{Bu_4NBF_4}$ = 0.1 M, E_o-E_{sw} = 200 mV, t = 22 °C. ᵃWithout addition of water. ᵇ$C^0_{H_2O}$ = 0.5 M.

To the best of our knowledge, the value of K_7 has not been determined in DMF, but the application of ¹H and ¹³C NMR spectroscopy shows that the equilibrium favors the keto form and has allowed us to estimate that K_7 is less than $2 · 10^{-3}$. Now, since the enol form is expected to be a much stronger acid than the keto form,[22-25] the acceleration of the protonation rate by addition of BASE⁻ can be rationalized as being due to BASE⁻ catalysis of the formation of HDEMH (eqn. 8). At this point, it is important to notice that the concentration of basic species in solution is different from zero even in the cases where BASE⁻ has not been added because the conjugate base, HDEM⁻, is produced during the protonation of A⁻ by H_2DEM or HDEMH. Since HDEM⁻ can as well catalyze the enolization of H_2DEM (eqn. 8′), we have in the general case the set of proton and electron transfer steps represented by equations 8–13.

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$$H_2DEM + BASE^- \underset{k_{-8}}{\overset{k_8}{\rightleftharpoons}} HDEMH + BASE^- \quad (8)$$
$$(K_8 = k_8/k_{-8})$$

$$H_2DEM + HDEM^- \underset{k'_{-8}}{\overset{k'_8}{\rightleftharpoons}} HDEMH + HDEM^- \quad (8')$$
$$(K'_8 = k'_8/k'_{-8})$$

$$A^- + H_2DEM \overset{k_9}{\rightarrow} AH^- + HDEM^- \quad (9)$$
$$(k_{10} \gg k_9)$$

$$A^- + HDEMH \overset{k_{10}}{\rightarrow} AH^- + HDEM^- \quad (10)$$

$$AH^- + A^- \overset{k_{11}}{\rightarrow} AH^- + A \quad (11)$$

$$AH^- + H_2DEM \overset{k_{12}}{\rightarrow} AH_2 + HDEM^- \quad (12)$$
$$(k_{13} \gg k_{12})$$

$$AH^- + HDEMH \overset{k_{13}}{\rightarrow} AH_2 + HDEM^- \quad (13)$$
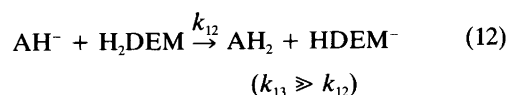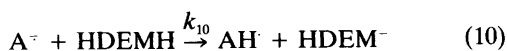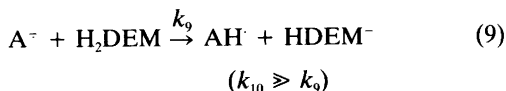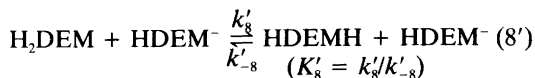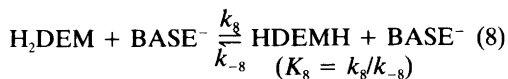
Obviously, K_8 and K'_8 are both equal to K_7. Under the assumption that the steady state approximation is valid for the three species AH^-, AH^- and HDEMH and at the same time, that the ratio between the rate constants for protonation of A^- and AH^- is independent of the nature of the acid, i.e. that $k_9/k_{12} = k_{10}/k_{13}$, we arrive at the general rate law for the reaction given in equation (14).

This rather complicated rate law may degenerate into one of two limiting cases depending on the competition between the two terms $k_{-8}C^o_{BASE^-} + k'_{-8}[HDEM^-]$ and $2k_{10}[A^-]$ or, in other words, on the basicity of A^- as reflected by k_{10}, since the term $k_{-8}C^o_{BASE^-} + k'_{-8}[HDEM^-]$ is independent of the nature of A. When $k_{-8}C^o_{BASE^-} + k'_{-8}[HDEM^-] \gg 2k_{10}[A^-]$ and, at the same time, advantage is taken of the equality $k_8/k'_8 = k_{-8}/k'_{-8}$, rate law (14) reduces to rate law (15). This situation corresponds to conditions where the interconversion of the keto and the enol forms can be regarded as a fast equilibrium prior to the rate determining proton transfer step. On the other hand, when $k_{-8}C^o_{BASE^-} + k'_{-8}[HDEM^-] \ll 2k_{10}[A^-]$, rate law

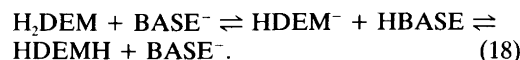(14) reduces to rate law (16), which in the limit when $k_8 C^o_{BASE^-} + k'_8[HDEM^-] \ll k_9[A^-]$, is further reduced to (17), corresponding to the direct proton transfer from the keto form to A^-. Comparison of the four rate laws, (14)–(17), leads to the prediction that the acceleration by BASE$^-$ depends on the basicity of A^-. For weakly basic A^-, the reaction follows rate law (15) and no effect of BASE$^-$ is expected. With increasing basicity of A^-, the rate of disappearance of A^- is successively described by rate laws (14), (16) and (17), predicting that the effect of BASE$^-$ passes through a maximum when $k_{-8}C^o_{BASE^-} + k'_{-8}[HDEM^-]$ and $2k_{10}[A^-]$ are of comparable magnitude, after which, the effect decreases and finally vanishes completely (rate law (17)). These predictions were tested experimentally by varying the basicity of the naphthalene anion radicals by proper substitution, and the results are shown in Figure 1, which demonstrates the acceleration caused by BASE$^-$ measured as the ratio between the $v_{0.8}$ values at $C^o_{BASE^-}$ equal to 10·7 and 1·8 mM. The lower concentration, 1.8 mM, was chosen instead of no addition of BASE$^-$ in order to minimize the influence of possible unknown basic species in the solution. The curve described by the experimental points is bell-shaped as predicted from rate laws (14)–(17), in support of the theoretical analysis. The catalytic effect of BASE$^-$ most likely includes the following acid-base equilibria[24] (eqn. 18):

$$-d[A^-]/dt = 2(k_9 + k_{10}K_8)[A^-][H_2DEM] \quad (15)$$

$$-d[A^-]/dt = 2(k_9[A^-][H_2DEM] + (k_8C^o_{BASE^-} + k'_8[HDEM^-])[H_2DEM]) \quad (16)$$

$$-d[A^-]/dt = 2k_9[A^-][H_2DEM] \quad (17)$$

$$H_2DEM + BASE^- \rightleftharpoons HDEM^- + HBASE \rightleftharpoons HDEMH + BASE^-. \quad (18)$$

Although the relative basicity of BASE$^-$ and HDEM$^-$, in general, does not affect the ratio between $[H_2DEM]$ and $[HDEMH]$, the absolute

$$-d[A^-]/dt = 2\left(k_9 + k_{10}\frac{k_8C^o_{BASE^-} + k'_8[HDEM^-]}{k_{-8}C^o_{BASE^-} + k'_{-8}[HDEM^-] + 2k_{10}[A^-]}\right)[A^-][H_2DEM] \quad (14)$$
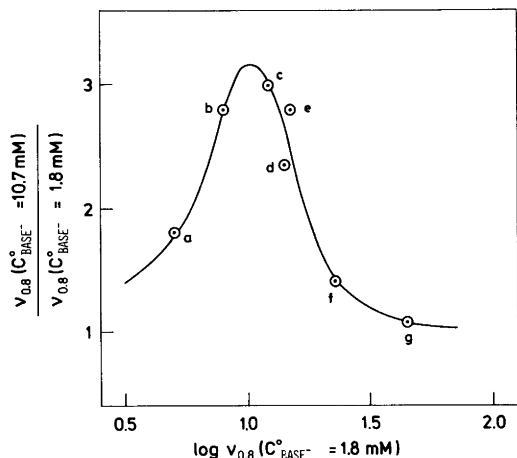
Fig. 1. The BASE⁻ acceleration factor,
$v_{0.8}$ ($C^o_{BASE^-}$ = 10.7 mM)/$v_{0.8}$($C^o_{BASE^-}$ = 1.8 mM), as a
function of the rate of disappearance of A⁻ for a
series of naphthalenes (average of two series of
measurements). C^o_A = 1 mM, $C^o_{H_2DEM}$ = 64 mM,
t = 22 °C. a: Naphthalene, b: 1-Methyl-, c: 2-Methoxy-,
d: 2-Methyl-, e: 2,6-Dimethyl-, f: 1-Methoxy- and
g: 1,5-Dimethyl-.

included in the solvent system. The data in the
third column of Table 1 were recorded to illus-
trate this point. Comparison of the data obtained
for protonation of 2-methoxynaphthalene anion
radical in "dry" DMF (column 2) with those ob-
tained in DMF containing water ($C^o_{H_2O}$ = 0.5 M,
column 3) shows that the rate enhancement in
going from $C^o_{BASE^-}$ = 0 mM to $C^o_{BASE^-}$ = 40.1 mM
has been reduced from a factor of 7 to a factor of
2 as a result of the inclusion of water in the sol-
vent. This reduced catalytic effect of BASE⁻ is
most likely associated with the formation of hy-
drogen-bonded complexes between water and
BASE⁻ which are expected to be less effective as
catalysts for the formation of the enol form,
HDEMH, than uncomplexed BASE⁻. The ki-
netic details of the application of H_2DEM and
similar carbon acids as proton sources during
protonation of anion radicals in aprotic solvents,
as well as the effect of other basic catalysts and
the structural consequences of adding water to
the solvent system are now being investigated.

Experimental

The voltammetric instrumentation, data acquisi-
tion techniques and solvent and supporting elec-
trolyte purification procedures were the same as
recently described.[4] During DCV experiments,
the value of E_o-E_{sw}, where E_{sw} is the switch poten-
tial, was adjusted to 200 mV to minimize the in-
fluence of background current caused by reduc-
tion of diethyl malonate. The aromatic and het-
eroaromatic substrates were all reagent grade
and used as received. NMR spectra were re-
corded on a JEOL FX90Q spectrometer. A 10 %
solution of diethyl malonate in DMF-d_7 was used
for the estimation of K_7. The ^{13}C chemical shifts
of this solution were the following: 167.3 ppm
(C=O), 61.4 and 41.8 ppm (CH_2) and 14.1 ppm
(CH_3). These signals were all attributed to the
keto form, H_2DEM. No other signals could be
detected, allowing for the evaluation of a maxi-
mum value of K_7 equal to $2 \cdot 10^{-3}$.

The apparently straightforward preparation of

values of the concentrations will be smaller than
expected if this equilibrium system is displaced in
favor of the products HDEM⁻ + HBASE. To as-
sure that additional complications were not intro-
duced in this way, we analyzed mixtures of
H_2DEM and Bu_4N^+, BASE⁻ in DMF by [13]C
NMR spectroscopy and found no evidence of the
presence of appreciable amounts of HDEM⁻ and
HBASE in the solutions.

In cases where no BASE⁻ is added to the volt-
ammetric solution, the two rate laws (14) and
(16) reduce to (19) and (20), respectively. These
rate laws show that the protonation of anion radi-
cals of intermediate acidity by H_2DEM are auto-
catalytic processes and rate data obtained for
anion radicals belonging to this class should con-
sequently be interpreted with great care.

The magnitude of the acceleration caused by
BASE⁻ was strongly diminished when water was

$$-d[A^-]/dt = 2\left(k_9 + k_{10}\frac{k_8'[HDEM^-]}{k_{-8}'[HDEM^-] + 2k_{10}[A^-]}\right)[A^-][H_2DEM]$$ (19)

$$-d[A^-]/dt = 2(k_9[A^-][H_2DEM] + k_8'[HDEM^-][H_2DEM])$$ (20)

Bu_4N^+, $HDEM^-$ was carried out by mixing equimolar amounts of Bu_4NOH (titrated 40 % aqueous solution) and diethyl malonate (distilled at reduced pressure) followed by evaporation of the water by a rotary evaporator. A stock solution of the salt was made from the resulting oil by dilution with DMF to a known volume. However, ^{13}C NMR spectra of solutions of the salt in DMF-d_7 and dimethyl sulfoxide-d_6 demonstrated that the product was Bu_4N^+, $EtOOCCH_2COO^-$ formed by hydrolysis of one of the ester groups. The evidence was the following: in addition to signals due to Bu_4N^+, the fully relaxed ^{13}C NMR spectrum in DMF-d_7 showed five signals of equal intensity at chemical shift values of 170.8 and 167.8 ppm (C=O), 59.5 and 46.9 ppm (CH_2) and 14.5 ppm (CH_3).

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