# Primary Deuterium Isotope Effect in the Proton Transfer Reaction between Ethyl Bis-(4-nitrophenyl)acetate and Tetramethylguanidine in Tetrahydrofuran Solvent

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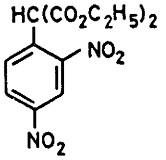
The reaction between ethyl bis-(4-nitrophenyl)acetate and tetramethylguanidine in tetrahydrofuran solvent gives a coloured product which decomposes under the influence of light to 4,4'-dinitrobenzophenone. The formation of the coloured material has been shown to take place in two steps. It is concluded that the first, faster step, which shows a primary deuterium isotope effect, $k_H/k_D$ 3.4 at 25 °C, is the proton transfer reaction yielding the carbanion of the substrate. A possible source of error in primary kinetic isotope effects is discussed.

THE extensive study of Caldin and his co-workers [1-4] on the primary deuterium isotope effects from carbon acids to the base tetramethylguanidine (TMG) (1) has provided a number of large isotope effects, $k_H/k_D > 30$, and has allowed the extensive body of kinetic data to be convincingly rationalized in terms of tunnelling of the proton through the potential energy barrier for the reaction. Analogous bases, with the same HN=C$<$ structure have also been shown to give large $k_H/k_D$ ratios.[4,5] In this work, we have attempted to test the generality of the phenomenon by studying the proton transfer to tetramethylguanidine from substrate molecules slightly different in structure to the α,4-dinitrotoluene extensively used by Caldin *et al.*[1-7]

Several substrate structures and many different solvents were tested for the reaction [equation (i)].

$$\mathrm{C{-}H} + \underset{(1)}{\mathrm{NH} = \mathrm{C[N(CH_3)_2]_2}} \rightleftharpoons \;>\!\mathrm{C}^{-}\{\mathrm{H_2NC[N(CH_3)_2]_2}\}^{+} \quad \text{(i)}$$

The 2,4-dinitrophenylmalonic ester (2) gave a coloured product instantly upon mixing with TMG, but the reaction was too fast to measure with a stopped-flow spectrophotometer. Ethyl diphenylacetate with TMG in chlorobenzene solvent gave no product with visible absorption, nor any absorption down to 200 nm, either because the reaction was very slow or because of an unfavourable equilibrium. Ethyl bis-(4-nitrophenyl)acetate and TMG gave a product with absorption maxima in the visible region in both chlorobenzene and tetrahydrofuran (THF), but no other solvent could be found which showed this reaction. The reaction was rather fast for stopped-flow spectrophotometry, but could be measured in THF solvent.



(2)

## EXPERIMENTAL

*Materials.*—THF was distilled from activated alumina and NaOH and received over Na–anthracene.[8] After at least 1 h over the Na–anthracene, the THF was redistilled, b.p. 66.0 °C, and stored in a brown bottle under nitrogen. Tetramethylguanidine was dried over KOH and distilled twice over BaO under nitrogen. The fraction boiling at 161—162° was collected.

Ethyl bis-(4-nitrophenyl)acetate was prepared from diphenylacetic acid by esterification according to the procedures of Vorländer [9] and Yost.[10] Diphenylacetic acid (10 g) and concentrated sulphuric acid (10 g) in absolute ethanol (60 ml) were heated at 95—98 °C and stirred for 48 h. The product was chilled in an ice-bath and the precipitated solid was filtered and washed with water. The ester was recovered in 61% yield, m.p. 57.5 °C. Nitration was accomplished by the method of Skerrett and Woodcock.[11] Ethyl diphenylacetate (7.15 g) was added slowly to fuming $HNO_3$ (45 ml) at −29 °C during 50 min. The mixture was stirred for an additional hour at this temperature and then poured into ice–water (350 ml). The product was extracted twice with $CHCl_3$ (*ca.* 200 ml) which was washed with water, 5% NaOH, and then dried over $CaCl_2$. Most of the chloroform was removed under vacuum leaving a thick oily solution to which a small amount of methanol was added. The product (2.8 g, 30%) precipitated immediately and was recrystallized from methanol, m.p. 131.5—132 °C (lit.,[10] 132—132.5 °C). N.m.r. and i.r. spectra confirmed the identity of the product.

Ethyl bis-(4-nitrophenyl)[$^2$H]acetate was prepared by repeated exchange, in a nitrogen atmosphere, of the substrate with $D_2O$–NaOD in THF, followed by neutralization with DCl. After seven exchanges, the recovered ester was recrystallized from methanol, m.p. 133—134 °C. The n.m.r. spectrum showed that the acidic hydrogen had been replaced by deuterium to an extent >97%.

*Kinetic Measurements.*—Pseudo-first-order rate constants $k_{obs}$ were measured for the reaction under conditions of a large excess of base using a Durrum stopped-flow spectrophotometer. The rate constants were evaluated using the Guggenheim method by a least squares computation. The second-order rate constants were derived from the slope of plots of $k_{obs}$ against base concentration.

*Preparation of Carbanion of Substrate.*—The substrate ester ($1.2 \times 10^{-3}$ mol) was treated with tetramethylguanidine (0.022 mol) in hexane–chloroform (5 : 1 v/v) under nitrogen. The mixture was stirred for 15 min at room temperature while protected from the light. After removal of the solvent and excess of base under vacuum, a dark blue oil was obtained. The n.m.r. spectrum of this product showed it to be a mixture of starting material and the carbanion $[(O_2NC_6H_4)_2CCO_2C_2H_5]^-$, with the latter as the minor constituent.

In order to obtain a more favourable equilibrium constant, the reaction was repeated in methanol–THF using sodium methoxide as base. After stirring for 10 min at 0 °C, the mixture was pumped dry at the same temperature. A dark blue-violet solid (74%) was obtained which the n.m.r. spectrum showed to be a mixture of methyl bis-(4-nitrophenyl)acetate, the carbanion corresponding to this compound, 4,4′-dinitrobenzophenone, and methoxide ion.

## RESULTS AND DISCUSSION

A mixture of ethyl bis-(4-nitrophenyl)acetate and tetramethylguanidine in THF solution with the base in large excess showed two maxima at λ 665 and 513 nm, with the molar absorptivity for the 665 nm peak 1.3 times that for the 513 nm peak. This coloured product decomposes rather quickly under the influence of light giving a final product which shows a single maximum at λ 292 nm.

If the coloured product is assumed to be the carbanion ion-pair, the equilibrium constant $K$ and the molar absorptivity $\varepsilon$ of the product can be calculated by the Benesi–Hildebrand [12] method using equation (ii) where

$$[S]/\text{o.d.} = 1/K[B]\varepsilon + 1/\varepsilon \qquad \text{(ii)}$$

[S] and [B] are the initial concentrations of the substrate and base and o.d. is the observed optical density. The optical density measurements at 665 nm derived from the infinity readings of kinetic runs carried out on the stopped-flow spectrophotometer fitted equation (ii) as illustrated in Figure 1. The intercept and slope, calculated by the least square method, gave $K$ 8 ± 1.3 dm$^3$ mol$^{-1}$ and $\varepsilon_{665}$ 2 800 ± 420 dm$^3$ mol$^{-1}$ cm$^{-1}$.

Kinetic measurements on the reaction showed two steps in the formation of the coloured product, the second-order rate constants of which differed by a factor of 200—800 according to the temperature. Since the faster first step showed a primary deuterium isotope effect and the second step did not, the former is assumed to be the proton transfer.

The rate constants for the first step for both the normal and deuteriated substrate are shown in Table 1. The pseudo-first-order rate constants $k_{obs}$ were determined for five or six different base concentrations. The second-order rate constant $k_f$ for the forward reaction and the first-order rate constant $k_b$ for the reverse reaction were determined from the slope and intercept respectively of plots of $k_{obs}$ *versus* $b$. The intercepts of the graphs $k_b$ show a considerable scatter, particularly those for the deuteriated substrate, which is much larger than the calculated standard deviations. These results can be considered, therefore, only as order of magnitude determinations. The isotope effects for the forward reaction are shown in Table 2.

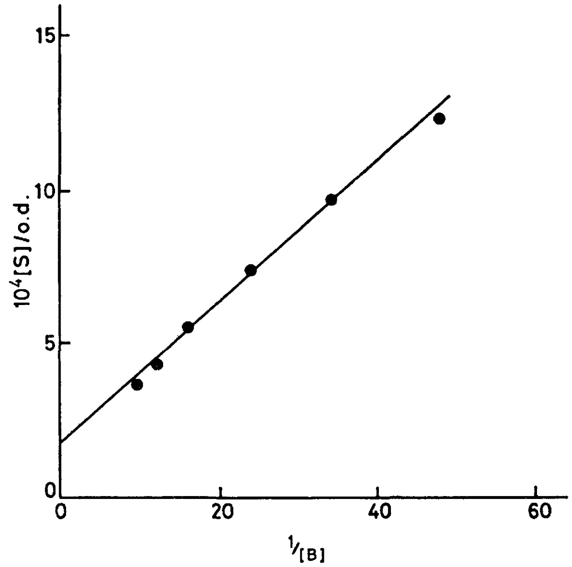


FIGURE 1 Plot of 1/[B] *vs.* [S]/o.d. for the reaction of ethyl bis-(4-nitrophenyl)acetate with tetramethylguanidine in tetrahydrofuran solvent at 25.2 °C

The slower second step was studied in the same manner, mostly with the deuteriated substrate. The second-order rate constants are shown in Table 3. The

TABLE 1

Rate constants for the reaction of ethyl bis-(4-nitrophenyl)acetate with tetramethylguanidine in tetrahydrofuran; the proton transfer step [a]

| Temp. (°C) | $10^3b$ | $k_{obs}/s^{-1}$ | $10^{-1}k_f$/ dm$^3$ mol$^{-1}$ s$^{-1}$ | $10^{-1}k_b/s^{-1}$ |
|---|---|---|---|---|
| (a) Normal substrate | | | | |
| 10.3 | 10.3—41.1 | 39.7—63.5 | 55 ± 9 | 4.1 ± 0.1 |
| 10.3 [b] | 10.3—41.4 | 41.1—66.3 | | |
| 15.4 | 13.2—39.5 | 58.0—80.2 | 84 ± 12 | 4.9 ± 0.3 |
| 19.6 | 13.2—52.7 | 76.7—120 | 106 ± 26 | 6.6 ± 0.7 |
| 25.1 | 9.2—45.9 | 101—167 | 218 ± 34 | 8.8 ± 0.7 |
| 29.7 | 9.9—24.8 | 122—168 | 322 ± 34 | 8.7 ± 0.6 |
| 34.8 | 5.0—19.9 | 112 187 | 490 ± 38 | 8.7 ± 0.5 |
| (b) Deuteriated substrate | | | | |
| 10.3 | 10.2—51.1 | 4.5—9.8 | 12.7 ± 0.7 | 0.3 ± 0.1 |
| 10.3 [b] | 20.5—51.1 | 5.5—10.3 | | |
| 15.4 | 13.1—52.6 | 19.8—29.0 | 23.1 ± 2.9 | 1.7 ± 0.1 |
| 20.0 | 13.1—52.6 | 23.5—34.6 | 39.4 ± 6.1 | 1.9 ± 0.1 |
| 25.2 | 9.2—36.7 | 34.7—55.4 | 63.9 ± 3.7 | 2.8 ± 0.2 |
| 29.9 | 5.0—25.0 | 75.6—93.1 | 91.4 ± 6.9 | 7.2 ± 0.1 |
| 35.1 | 5.0—14.9 | 33.1—49.6 | 156 ± 27 | 2.8 ± 0.4 |

[a] Initial concentration of substrate, 2 × $10^{-4}$—4.4 × $10^{-4}$M; the limits quoted for $k_f$ and $k_b$ are standard deviations. [b] Measurements carried out at 665 nm, except at 10.3 °C when a second determination was made at 513 nm.

TABLE 2

Isotope effects for the proton transfer between ethyl bis-(4-nitrophenyl)acetate and tetramethylguanide in THF

| $T$/°C | 10 | 15 | 20 | 25 | 30 | 35 |
|---|---|---|---|---|---|---|
| $k_H/k_D$ | 4.3<br>±0.7 | 3.6<br>±0.5 | 2.7<br>±0.7 | 3.4<br>±0.5 | 3.5<br>±0.4 | 3.1<br>±0.2 |

TABLE 3

Second-order rate constants for the second step in the reaction between ethyl bis-(4-nitrophenyl)acetate and tetramethylguanidine in THF

| Temp. (°C) | $10^3b$ | $10^2k_{obs}/s^{-1}$ | $k_2$/ dm$^3$ mol$^{-1}$ s$^{-1}$ |
|---|---|---|---|
| 10.3 | 12.9—45.9 | 7.7—12.9 | $1.6 \pm 0.4$ |
| 10.3 * | 12.9—45.9 | 6.9—13.9 | $2.1 \pm 0.3$ |
| 15.3 | 13.1—65.7 | 4.6—15.8 | $2.1 \pm 0.2$ |
| 19.7 | 13.1—39.4 | 7.2—14.6 | $2.7 \pm 0.3$ |
| 25.0 | 12.9—36.7 | 10.8—20.3 | $3.9 \pm 0.2$ |
| 29.9 | 5.0—25.0 | 2.5—12.2 | $4.4 \pm 0.6$ |
| 34.8 | 7.0—25.0 | 5.6—15.1 | $5.6 \pm 0.7$ |

* Measurements carried out at 665 nm; except at 10.3 °C when a second determination was made at 513 nm.

TABLE 4

Activation parameters for the reaction between ethyl bis-(4-nitrophenyl)acetate and tetramethylguanidine in THF

| | Proton transfer step | Second step |
|---|---|---|
| $\Delta H_H^\ddagger$/kcal mol$^{-1}$ | $15.0 \pm 1$ | $8.3 \pm 0.5$ |
| $\Delta H_D^\ddagger$/kcal mol$^{-1}$ | $16.4 \pm 0.5$ | |
| $\Delta S_H^\ddagger$/cal mol$^{-1}$ K$^{-1}$ | $6.8 \pm 3.3$ | $-28.3 \pm 1.6$ |
| $\Delta S_D^\ddagger$/cal mol$^{-1}$ K$^{-1}$ | $9.3 \pm 1.6$ | |

1 cal ≡ 4.184 J.

rate constant was determined at one temperature for the normal substrate and found to be the same as that for the deuteriated compound, within experimental error. This, together with the fact that the infinity absorbance was identical for the two compounds, indicates that this step is the same reaction in each case. This reaction is, therefore, one which results in no significant change in absorption spectrum and could be a further reaction of the carbanion, *e.g.* oxidation by oxygen of the anion to a radical anion.

The rate constants in Table 3 were used to derive the activation parameters in Table 4, which also shows those derived from the second-order rate constants in Table 1.

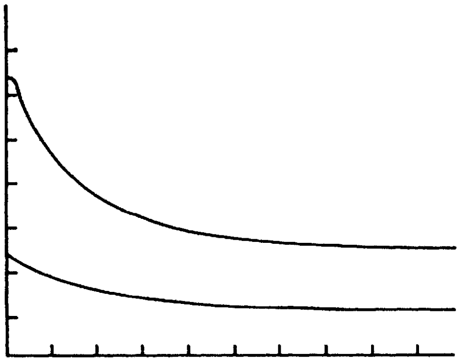


FIGURE 2 Normal substrate, initial concentration 3.7 × $10^{-4}$M, TMG 4.66 × $10^{-2}$M, temperature 19.9 °C. Vertical axis, 0—100% transmittance. Horizontal axis, 5 ms per division (upper curve), 2 s per division (lower curve)

The form of a kinetic run for the normal substrate is shown in Figure 2, from which it can be seen that the first step accounts for the major part of the coloured product. For the deuteriated substrate, the first step produces a smaller proportion of the final colour, as shown in Figure 3, and as the temperature is increased, the second step becomes increasingly dominant. If the difference between the rate constants for the first and second steps were not as large as it is in this case, *i.e.* a factor of 200—800, it would be possible to dismiss the first step of the deuteron transfer as being due to residual hydrogen in the substrate and to compare the first step of the proton reaction with the second step of the deuteron reaction. As can be seen from Figure 3, when the time base is set at an appropriate value (2 s per divsion) to measure the second step, the first step is not observed at all. With a smaller difference in rate between the first and second steps, the first step would appear as a small irregularity at the beginning of the reaction trace, which could be dismissed without attempting to measure its rate constant. This would yield an abnormally large apparent isotopic rate ratio.

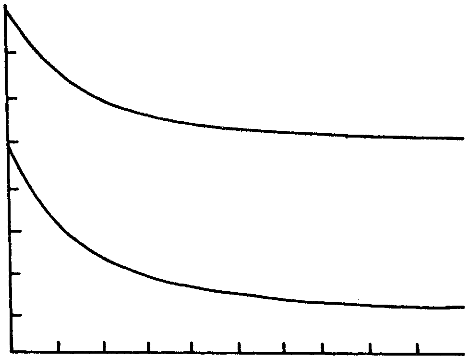


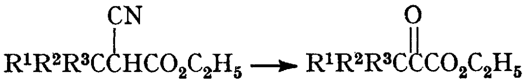
FIGURE 3 Deuteriated substrate, initial concentration 3.7 × $10^{-4}$M, TMG 6.57 × $10^{-2}$M, temperature 15.4 °C. Vertical axis, 0—100% transmittance. Horizontal axis, 20 ms per division (upper curve), 2 s per division (lower curve)

Evidence for an additional intermediate in a proton transfer, which produces no observable change in the absorption spectrum has been noted by Caldin *et al.*[13] It is certainly possible for two intermediate products of similar structure to have indistinguishable absorption spectra and, if the rate constants are not markedly different, it would be very difficult to prove by direct measurement that the reaction is not proceeding *via* a single step.

This reaction, therefore, demonstrates a type of reaction sequence which might, if the reaction activation parameters were somewhat different, give rise to an abnormally large false primary deuterium isotope effect. Rogne has recently demonstrated[14,15] how such a situation could also result from H–D exchange. While it is a distinct possibility that some abnormally large isotope effects may result from reaction mechanisms more complex than the rate measurements indicate, it cannot be concluded that this is generally the case. Other tests of internal consistency are available. In the present reaction, the value of $\Delta H_D^\ddagger$ exceeds that of $\Delta H_H^\ddagger$ by 1.4 ± 0.6 kcal $mol^{-1}$ consistent with standard zero-point energy theory. On the other hand, $\Delta H^\ddagger$ for the second step is 6.7 kcal $mol^{-1}$ less than $\Delta H_H^\ddagger$. Thus, confusion of the second step with the deuteron transfer step would not only have yielded a very high rate ratio, but also a very large isotope effect on $\Delta H^\ddagger$ in the wrong direction. However, the lower $\Delta H^\ddagger$ value for the second step compared to the proton transfer step may not be a general result. In fact, $\Delta H_H^\ddagger$ and $\Delta H_D^\ddagger$ are rather high for proton and deuteron transfer reactions. However, these may be accounted for in terms of the strong solvation shell which must exist around the ester substrate in THF solvent. The breaking down of this shell in order to form the transition state of the proton transfer step would be expected to give a large enthalpy and a positive entropy of activation.

*Reaction Pathway*.—Attempts to isolate the products of the reaction (see Experimental section) yielded mixtures of the starting material, carbanion, and 4,4′-dinitrobenzophenone. The latter, isolated from the mixture which had been allowed to come in contact with air, showed a u.v.–visible spectrum when run against a reference of tetramethylguanidine in THF which had a single peak at 292 nm. Thus, 4,4′-dinitrobenzophenone is confirmed as the final product of the reaction.

The reaction sequence is envisioned as the initial formation of the carbanion by a base-induced proton abstraction. In the presence of excess base and an electron acceptor, *e.g.* molecular oxygen or a peroxide, the carbanion is converted to a second intermediate probably, a radical anion, which decomposes to 4,4′-dinitrobenzophenone. A similar type of reaction sequence has been noted by Rabjohn and Harbert [16] for the base catalysed autoxidation of (3) to (4) in tetrahydrofuran solvent.



$$R^1R^2R^3C\overset{CN}{\overset{|}{C}}HCO_2C_2H_5 \longrightarrow R^1R^2R^3C\overset{O}{\overset{\|}{C}}CO_2C_2H_5$$

(3) (4)

We have shown that the carbanion is formed under reasonably similar conditions to the reaction which has been studied kinetically, but to prove the identity of the product of each reaction step by direct observations, would require techniques not available to us.

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