

RATE OF TRITIUM EXCHANGE IN DIETHYL METHYL- d_3 -MALONATE- t AND DIETHYL MALONATE- d,t IN BUFFERED AQUEOUS SOLUTIONS

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INTRODUCTION

Secondary kinetic isotope effects related to hyperconjugation and re-hybridization are well known, principally from extensive studies of the influence of deuterium substitution on the reaction rate in solvolytic displacement reactions.

There now exists ample evidence that, because of a slightly greater electron density near the carbon atom in a carbon-deuterium bond, compared to a carbon-hydrogen bond, deuterium is effectively electron-donating relative to hydrogen¹⁻⁴.

One of the principal difficulties in assessing the relative contribution of the inductive effect on the reactivities of deuterium-labelled compounds arises from the fact that in carbonium ion reactions the other possible sources of the secondary hydrogen isotope effect, *i.e.* hyperconjugation and re-hybridization, being more pronounced and of opposite direction, outweigh the influence of induction.

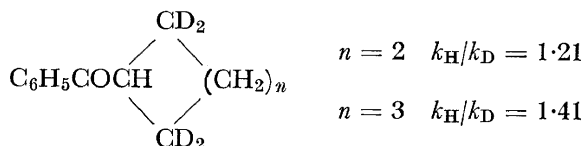
The inductive effect of deuterium was considered as being responsible for the observed inverse isotope effect ($k_H/k_D = 0.93$) in the reaction of methyl *p*-bromobenzenesulphonate with triethylamine having deuterium in one of the methylene groups⁴. Streitwieser also observed³ that the solvolysis of di-(phenyl-2,3,4,5,6- d_5)-methyl chloride in aqueous acetone is about 17 per cent faster than that of benzhydryl chloride.

Polar reactions which involve negatively charged intermediates or transition states are in some respect more suitable for the study of the influence of the inductive effect of deuterium on reaction rates. Primary hydrogen isotope effects related to carbanion formation proved to be a great help for the elucidation of the rate-determining step in a number of elimination reactions and both acid- and base-catalysed enolization of ketones. However, the possible interference of secondary hydrogen isotope effects was not studied in many cases.

In terms of a positive inductive effect of deuterium Halevi⁵ explained the observed reductions of the acid ionization constant of α -dideuterophenylacetic acid and the α -dideuterobenzylammonium ion.

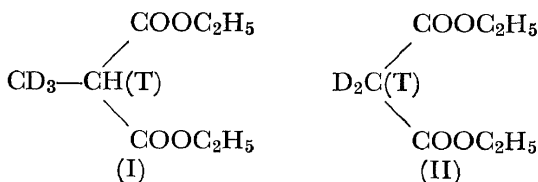
Emmons and Hawthorne⁶ studied the effect of deuterium substitution on the rate of acid- and base-catalysed enolization of cycloalkyl phenyl ketones.

With deuterium in the β position secondary isotope effects ranging from 20 to 40 per cent were observed:



These results have been explained as possibly due to the stabilization of the enol form by hyperconjugation involving the β -hydrogen atoms.

In connection with this problem we wish to report some measurements of the rate of tritium exchange in diethyl methyl-d₃-malonate-t (I) and diethyl malonate-d,t (II) in buffered aqueous solutions.



If, in the exchange reaction, the formation of the corresponding carbanions is rate-determining, these compounds would provide simple models for the study of the inductive effect of deuterium as compared to hydrogen.

METHODS AND RESULTS

Diethyl methyl-d₃-malonate was prepared in the usual manner from diethyl malonate and methyl-d₃ bromide. The ester was dissolved in a mixture of ethyl alcohol and tritiated water and in this way the residual acidic hydrogen was partly substituted for tritium.

About 50 mg of the carefully purified tritiated ester were then dissolved in aqueous citric acid/disodium hydrogen phosphate buffer solution (50 ml, 0.3 M, pH 6.8) and the exchange rate followed at 40°. Samples were withdrawn at regular time intervals, extracted with toluene and the extracts carefully dried. The activity of aliquots of this solution was determined with a Tri-Carb liquid scintillation spectrometer using the standard PPO/POPOP toluene solution as the scintillator. From the decrease of the activity of samples as a function of time, first-order rate constants for the tritium exchange reaction were calculated by the graphical method and also with the aid of the IBM 7090 computer. The analogous experiment was also performed with tritiated diethyl methylmalonate.

The obtained results are summarized in *Tables 1* and *2*.

From these results it can be seen that the rate of tritium exchange is the same for both compounds. This demonstrates that the introduction of deuterium in the β -position with respect to the reaction centre does not, within the limits of error, affect the reaction rate.

The purpose of a second series of experiments was to find out to what extent the substitution of deuterium at the reaction centre might affect the reaction rate. Obviously, in this case the rate of exchange of tritium in the

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deuterated diethyl malonate (II) has to be measured in deuterium oxide solution and not in water. Therefore, it was necessary to obtain some data about the possible influence of the solvent (ordinary and heavy water, respectively) on the exchange rate.

Thus, tritiated diethyl methylmalonate was dissolved in an H_2O and D_2O buffer solution respectively and the rate of tritium exchange determined in the same manner as described previously. The results presented in Table 3 demonstrate that the exchange rate was practically the same in both solvents.

For the second series of experiments diethyl malonate was labelled with

Table 1. Rate of tritium exchange of diethyl methylmalonate- t in buffered aqueous solution at 40°

Experiment no.	$k \times 10^5 \text{ (sec}^{-1}\text{)}$	
	Graphically	IBM 7090
1	3.79	3.77
2	3.54	3.50
3	3.71	3.85
4	3.74	3.79
5	3.88	3.86
6	3.86	3.85
7	4.54	4.80
8	4.24	4.41
9	4.40	4.46
10	3.90	3.94
11	3.41	3.71
12	3.75	3.72
Mean	3.89 ± 0.034	3.97 ± 0.12

Table 2. Rate of tritium exchange in diethyl methyl- d_4 -malonate- t in buffered aqueous solution at 40°

Experiment no.	$k \times 10^5 \text{ (sec}^{-1}\text{)}$	
	Graphically	IBM 7090
1	4.18	4.18
2	4.28	4.15
3	3.42	3.92
4	3.58	3.70
5	5.73	3.59
Mean	3.83 ± 0.052	3.90 ± 0.037

Table 3. Rate of tritium exchange in diethyl methylmalonate- t in buffered H_2O and D_2O solutions at 40°

Experiment no.	$k \times 10^5 \text{ (sec}^{-1}\text{)}$ in H_2O	Experiment no.	$k \times 10^5 \text{ (sec}^{-1}\text{)}$ in D_2O
1	3.78	7	3.38
2	3.42	8	3.85
3	3.45	9	3.66
4	3.52	10	3.41
5	3.23	11	3.36
6	3.37		
Mean	3.48 ± 0.079		3.53 ± 0.03

deuterium by repeated exchange with deuterium oxide in tetrahydrofuran solution. The purified ester contained the theoretical amount of deuterium. Tracer amounts of tritium were introduced into the molecule by the same procedure using tritiated water instead of deuterium oxide. The rate of tritium exchange for the deuterium-labelled ester was followed in buffered deuterium oxide solution at 25° and the rates for the corresponding hydrogen compound in buffered aqueous solution. The samples were treated in the manner described earlier and the first-order rate constants were determined graphically. The results are given in *Table 4*.

Table 4. Rate of tritium exchange in diethyl malonate-t and diethyl malonate-d,t in buffered H₂O and D₂O solutions at 25°

Compound	$k \times 10^4 \text{ (sec}^{-1}\text{)}$	k_H/k_D
H ₂ C(CO ₂ Et) ₂	13.4	10.27
	13.4	
	14.1	
	13.2	
	14.3	
	14.3	
	13.5	
	15.3	
	13.2	
	13.5	
	Mean 13.86 ± 0.02	
D ₂ C(CO ₂ Et) ₂	1.388	10.27
	1.332	
	1.335	
	Mean 1.351 ± 0.10	

DISCUSSION

From the experimental evidence presented in this paper only tentative conclusions regarding the involved reaction mechanism can be given.

The absence of an isotope effect in the case of diethyl methyl-d₃-malonate indicates that a possible inductive effect of deuterium, if operative in this system at all, is certainly less than 10 per cent. For the final answer to this question we have to wait for results from experiments where the rate of reaction will be followed by bromination, which is a more precise method than the measurement of radioactivity with the scintillation counter.

A mechanistic explanation of the second set of results is somewhat more difficult. The observed large isotope effect ($k_H/k_D = 10.27$) indicates that we are dealing with a combined primary and secondary hydrogen isotope effect. The primary effect cannot be explained without invoking some speculation. The cleavage of the carbon-deuterium bond in the rate-determining step should yield a tritium-labelled carbanion. It remains to be explained how this intermediate then rapidly loses tritium. To clarify this situation, further experiments are now in progress.

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