

METHYL- d_3 ISOTOPE EFFECTS AND THE ORIGIN OF α -METHYL SUBSTITUENT EFFECTS

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Abstract—The kinetic isotope effects on the solvolysis of a series of 1-methyl- d_3 compounds was determined. A linear correspondence between α -methylsubstituent effects and methyl- d_3 isotope effects is presented and discussed.

THE kinetic isotope effect on the solvolysis of 1-methyl- d_3 -cyclobutyl chloride and cyclopropylmethyl- d_3 -carbinyl chloride was recently reported to be significantly smaller than that observed in the solvolysis of other β -deuterated halides.¹ The hypothesis was advanced that secondary β -isotope effects might be used as a criterion for charge delocalization such as occurs in the formation of non-classical carbonium ions.

In view of Shiner's demonstration that secondary β -deuterium isotope effects arise predominantly through a hyperconjugative mechanism² a comparison of the Me and Me- d_3 effects should provide further insight into the origin of the large rate enhancements resulting from Me substitution on the reaction center in carbonium ion reactions.

The determination of the kinetic isotope effect on the solvolysis of a series of 1-methyl- d_3 compounds including ones thought to yield classical and non-classical ions was undertaken. The results of this study are presented here.

RESULTS

Methylcyclopentyl chloride (Ia), methylcyclohexyl chloride (IIa) and 2-methyl-*exo*-2-norbornyl chloride (IIIa) and their Me- d_3 analogues Ib, IIb and IIIb were prepared by well-known procedures involving addition of the appropriate MeMgBr to the corresponding ketone followed by treatment of the resultant alcohol with anhydrous hydrogen chloride.

The rates of solvolysis of I–IIIa and b were determined in "80% aqueous ethanol" using an automatic recording titrator and the results are presented in Table 1. The rate of solvolysis of Ia at 25.00° and 35.00° has been reported as 3.67×10^{-4} and $11.3 \times 10^{-4} \text{ sec}^{-1}$,³ respectively, in good agreement with our values.

DISCUSSION

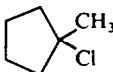

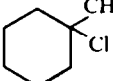
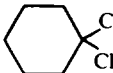
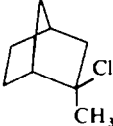
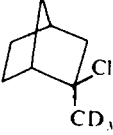
The Me- d_3 isotope effects for I, II, and III are all nearly equivalent and perhaps smaller than might have previously been expected. For non-cyclic aliphatic compounds, Me- d_3 isotope effects range from 1.16 for hydrolysis of isopropyl bromide⁴

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to 1.40 for the alcoholysis of 2,4,4-trimethyl-2-chloropentane-1-d₃.⁵ Compounds in which electron delocalization is thought to be significant show reduced Me-d₃ isotope effects; for 2-(*p*-methoxyphenyl)2-chloropropane the Me-d₃ isotope effect is 1.13⁶ while for methylcyclobutyl chloride the Me-d₃ isotope effect is 1.09.¹

The evidence for non-classical electron delocalization in the solvolytic intermediate from 2-methyl-*exo*-2-norbornyl chloride is not entirely unequivocal⁷ but does have considerable support. We had hoped to see the effect of non-classical ion formation reflected in the Me-d₃ isotope effect. The data of Table 1 show no abnormality for 2-methyl-*exo*-2-norbornyl chloride in comparison to methylcyclopentyl chloride or methylcyclohexyl chloride.

TABLE I. RATE OF SOLVOLYSIS OF 1-METHYL AND 1-METHYL-d₃-CYCLOALKYL CHLORIDES IN "80% AQUEOUS ETHANOL"^a

Compound	Temp. °C	$k \times 10^{-4} \text{ sec}^{-1}$	k_H/k_D
Ia 	35.00	11.75 ± 0.07	
	25.00	3.810 ± 0.05	
Ib 	35.00	9.697 ± 0.022	1.21 ± 0.01
	25.00	3.041 ± 0.030	1.25 ± 0.03
IIa 	60.00	2.376 ± 0.008	
IIb 	60.00	1.966 ± 0.014	1.21 ± 0.01
IIIa 	35.00	91.00 ± 0.93	
	25.00	31.00 ± 0.24	
IIIb 	35.00	73.34 ± 0.59	1.241 ± 0.024
	25.00	25.34 ± 0.14	1.223 ± 0.017

^a Uncertainties are standard errors, all are for three separate determinations.

It is common knowledge that α -Me substituents greatly accelerate S_N1-type reactions.⁸ How much of the accelerative effect of α -Me groups in S_N1 reactions is to be attributed to induction, how much to hyperconjugation and how much to steric acceleration is not definitely known.

The inductive effects of alkyl groups, although perhaps not negligible, are certainly much smaller* than those associated with other common substituent groups. If, for

* $K_{a_{\text{CH}_3\text{CO}_2\text{H}}} = 1.77 \times 10^{-5}$; $K_{a_{\text{CH}_3\text{CH}_2\text{CO}_2\text{H}}} = 1.34 \times 10^{-5}$; $K_{a_{\text{FCH}_2\text{CO}_2\text{H}}} = 2.59 \times 10^{-3}$.⁹

illustrative purpose, one assumes $\rho^* = -4$ for a limiting ionization in the secondary series* and that inductive effects decrease by a factor of 3 per intervening CH₂ group ($\sigma_{\text{C}_6\text{H}_5}^* = 0.60$; $\sigma_{\text{C}_6\text{H}_5\text{CH}_2}^* = 0.22$; $\sigma_{\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2}^* = 0.08$: Ref. 10 p. 619), the α -Me substitution should produce an inductive rate increase of about 1 order of magnitude ($\sigma_{\text{CH}_3}^* = 0.0$; $\sigma_{\text{CH}_3\text{CH}_2}^* = -0.10$). While the exact magnitude (and perhaps even the direction) of this effect may be open to question, it is obvious that the inductive effect can account for only a small fraction of the observed differences in rate between secondary and tertiary derivatives (5 to 6 powers of 10) upon α -Me substitution.

Estimation of the portion of the α -Me substituent effect ascribable to steric acceleration (B-strain effect) is much more difficult.¹¹ For secondary derivatives, non-bonded interaction strain has been stated¹² not to give rise to very pronounced rate effects, amounting to only 10¹ or at most 10², for relatively uncrowded secondary tosylates. For tertiary derivatives, steric acceleration should be much larger and dependent on the structural details of the derivative.

The theoretical approach of Bigeleisen and Mayer¹³ when applied to secondary isotope effects shows that these result from changes in the force field at the site of isotopic substitution.¹⁴ These changes are commonly discussed in terms of re-hybridization, hyperconjugation and non-bonded interactions.

The main difficulty in interpreting secondary hydrogen isotope effects lies in differentiating and evaluating the different factors influencing the overall effect.¹⁵ The so-called "steric isotope effect", resulting in a lower average steric potential energy due to the smaller mean-square amplitude of the C—D bond has been experimentally demonstrated by Mislow^{16a} and Melander.^{16b} From the available data, it seems that such an effect can only be expected in reactions where the transition state is extraordinarily strained as a result of large C—D bond deformations, i.e. where the changes in potential function brought about by an increase in the force field produces a change in zero point energy. This is certainly not the case for the compounds considered here.†

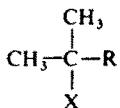

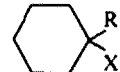
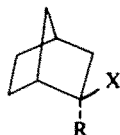
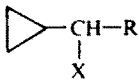
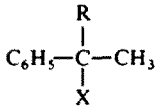
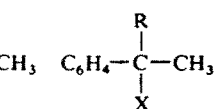
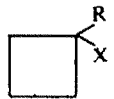
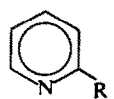
Experimentally, perhaps the most elusive cause of secondary isotope effects is the larger effective electron releasing power of a C—D bond relative to a C—H bond due to the shorter mean bond lengths in the deuterated compounds resulting from anharmonicity. The magnitude of this factor in rate processes generating anionic or cationic intermediates¹⁷ has been shown to be immeasurably small and should be unimportant in the cases considered here. Both the non-additivity of the kinetic isotope effects in solvolytic reactions of β -deuterated compounds and the conformational dependence of these isotope effects have provided clear-cut evidence for hyperconjugation as the source of these effects.²

If the origin of the α -Me substituent effect were also predominantly due to hyperconjugation, then a correspondence should exist between α -Me substituent effects and Me-d₃ isotope effects. The available data on Me substituent effects and Me-d₃ isotope effects for a variety of compounds are presented in Table 2. As shown in

* The acetic acid solvolysis of secondary brosylates has $\rho^* = -3.49$.¹⁰

† Recently, it has been suggested that "the dominant factor in the secondary isotope effect may be steric in origin" (H. C. Brown *et al.*, *J. Am. Chem. Soc.* **88**, 2514, 2520 (1966)). In our opinion such a suggestion overestimates the importance of changes in the potential function in solvolytic reactions.

TABLE 2. METHYL AND METHYL-d₃ RATE EFFECTS

	Compound	$k_{\text{CH}_3}/k_{\text{CD}_3}$	$k_{\text{CH}_3}/k_{\text{H}}$
1.		1.33 ^a	10 ^{5.2b} 10 ^{6c}
2.		1.21 ^d 1.25	27,600 ^e
3.		1.21 ^d	22,800 ^f
4.		1.22 ^d	18,800 ^e
5.		1.18 ^b	4160 ^b
6.		1.17 ⁱ	1800 ^j
7.	$p\text{-OCH}_3$ 	1.13 ^k	120 ^l
8.		1.09 ^b	130 ^b
9.		0.970 ^m	0.463 ^m

^a V. J. Shiner, Jr., B. L. Murr and G. Heinemann, *J. Am. Chem. Soc.* **85**, 2413 (1963).

^b F. R. Jensen and R. J. Ouellette, *Ibid.* **85**, 363 (1963) for the ionization of alkylmercuric salts in acetic acid at 75°.

^c Estimated for bromides in formic acid at 100°, A. Streitwieser, Jr., *Chem. Revs.* **56**, 571 (1956).

^d This work.

^e J. D. Roberts, L. Urbanek and R. Armstrong, *J. Am. Chem. Soc.* **71**, 3049 (1949); see also Ref. 3 for chlorides in 80% ethanol at 85.00°.

^f J. D. Roberts and V. C. Chambers, *Ibid.* 73, 5034 (1951) and Ref. e; chlorides in 50% ethanol at 95.00°.

^g J. D. Roberts and W. Bennett, *Ibid.* 76, 4623 (1954) and this work; chlorides in 80% ethanol at 85.00°.

^h See Ref. 1 (this paper).

ⁱ E. S. Lewis, R. R. Johnson and G. M. Coppinger, *Ibid.* 81, 3140 (1959); isotope effect for *p*-CH₃C₆H₄CH(Cl)CD₃ in 80% acetone at 50°.

^j See Ref. 21 (this paper).

^k V. J. Shiner, Jr., personal communication; isotope effect for *p*-CH₃OC₆H₄CHCD₃ in 93% acetone at 25°.

Cl

^l Y. Okamoto, Ph.D. thesis, Purdue University (1958). Rates in 93% acetone at 25° by interpolation between 90% and 94.8% acetone.

^m H. C. Brown and G. J. McDonald, *J. Am. Chem. Soc.* 88, 2514 (1966), for the reaction of pyridine bases with methyl iodide in nitrobenzene at 25°.

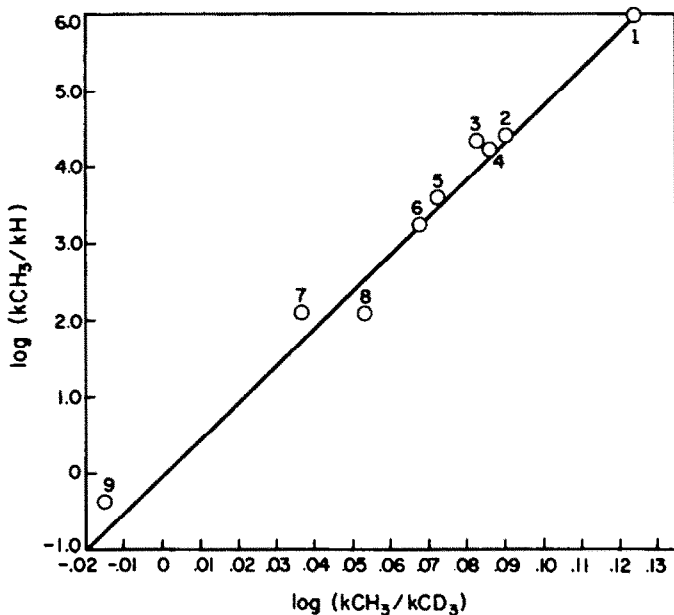


FIG. 1 α-Methyl substituent effects versus methyl-d₃ isotope effects; numbers refer to compounds of Table 2.

Fig. 1, such a free-energy relationship does indeed exist for reactions of a variety of compounds.*

If α-Me substituent effects were predominantly steric in origin, such a correlation would not be expected. Cases in which the α-Me substituent effect is enhanced by a complimentary steric acceleration should appear as a large vertical displacement

* This comparison is permitted since the deuterium substitution in the methyl group does not change the electronic partition functions. However, comparisons of >C-CH₃ effects with >C-D effects are not allowed.

from the line in Fig. 1; none of the compounds studied here provide support for such an effect.

One can also conclude that the use of Me-d₃ isotope effects as a criterion for anchimeric assistance is no more useful than the α-Me substituent effect. If the magnitude of an α-Me substituent effect can be argued to be consistent with a proposed structure for an intermediate, then in a similar fashion the Me-d₃ isotope effect can be explained.

EXPERIMENTAL

M.p.s are uncorrected. IR spectra were taken with a Perkin Elmer Model 421 spectrometer; NMR spectra were taken with a Varian A-60 spectrometer. All Me-d₃ alcohols were prepared analogously to the undeuterated compounds using samples of Me-d₃-bromide from the same batch. A Radiometer Copenhagen Titrigraph TTT-1 was used in the determinations of the rate constants for solvolysis in 80% aqueous EtOH (V:V).

Methyl-d₃-bromide. Diethyl malonate-d₄ was prepared by repeated exchange of diethyl malonate in D₂O-dioxan¹⁸ and thermally decarboxylated to AcOH-d₄.¹⁹ Methyl-d₃-bromide was prepared from the AcOH-d₄ by the Hunsdiecker reaction.²⁰ From the analysis of the NMR spectrum of 1-phenylethanol-2,2,2-d₃ prepared by the addition of Me-d₃-MgBr to benzaldehyde, the MeBr was found to be 94.2% deuterated.

Methylcyclopentanol. The addition of MeMgBr to cyclopentanone gave methylcyclopentanol b.p. 60–64° (50 mm); m.p. 30–32° (lit.³ m.p. 32–33°). Low temp recrystallization from pentane gave a product of >96% purity (VPC analysis).

Methylcyclopentyl chloride. Treatment of methylcyclopentanol with dry HCl gave methylcyclopentyl chloride in ~90% yield; b.p. = 65–67° (~120 mm); n_D²⁰ = 1.4455 (lit.³ 1.4467).

Methylcyclohexanol. The addition of MeMgBr to cyclohexanone gave an 80% yield of methylcyclohexanol, b.p. = 68–72° (25 mm)³. Low temp recrystallization from pentane gave a product of >98% purity (VPC analysis).

Methylcyclohexyl chloride. Treatment of methylcyclohexanol with dry HCl gave methylcyclohexyl chloride in ~90% yield; b.p. = 82–84° (100 mm); n_D²⁰ = 1.4564 (lit.³ 1.4578).

2-Methyl-endo-2-norbornanol. The addition of MeMgBr to norbornanone gave 2-methyl-endo-2-norbornanol, m.p. 32–32.5° (lit. 34°).^{7c}

2-Methyl-exo-2-norbornyl chloride. Treatment of 2-methyl-endo-2-norbornanol with dry HCl²¹ gave 2-methyl-exo-2-norbornyl chloride. (Purity by titration 98%, m.p. 22–25°).

Analysis of methyl-d₃-cyclohexyl chloride. Integration of the NMR spectrum of methyl-d₃-cyclohexyl chloride vs. dimethoxyethane standard indicated 90 ± 5% methyl deuteration.

2-Methyl-d₃-endo-2-norbornanol. Deuterium analysis by the falling drop method indicated 93.7% deuteration.

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