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A SECONDARY KINETIC ISOTOPE EFFECT IN CONFORMATIONAL RACEMIZATION[1]

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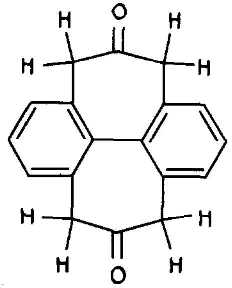
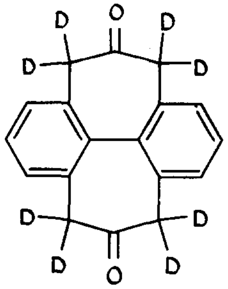
RECENT studies of secondary kinetic isotope effects have focussed on reactions which involve bond making and breaking at or near the site of isotopic substitution. We have now observed a mass effect in a purely conformational change: the racemization of diketones I and II.



I



II

In connection with our work on doubly bridged biphenyls[2] we had occasion to prepare I, m. p. 223-224° (under nitrogen),

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[1] Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the partial support of this research, and to the Alfred P. Sloan Foundation for fellowship support (K. M.).

[2] K. Mislow and M. A. W. Glass, J. Am. Chem. Soc. 83, 2780 (1961).

$\lambda\lambda_{max}^{cyclohexane}$ 228 mμ (ε 43,500), 257 mμ (ε 13,250), 291 mμ (shoulder, ε 1,650), 301 mμ (ε 2,700), 309 mμ (ε 2,900), 318 mμ (ε 1,030). The diketone was optically activated by partial asymmetric reduction[3] and was found to racemize in o-xylene according to the expression $k_1 = 10^{14.5} \exp(-31/RT)$ $sec.^{-1}$ The octadeuterio derivative II was prepared conventionally by successive exchanges with 99.5% D_2O/dioxane containing Na_2CO_3 and was optically activated as described for I. Compound II analyzed for 7.8 atoms of D per molecule (falling drop method) and its NMR spectrum displayed no proton resonance signal in the aliphatic region, in contrast to I, which exhibited an intense singlet at $\tau = 6.43$ (the structurally related dioxepin[2] and dithiepin[2] both feature spin coupled methylene quartets, $J_{AB} \sim 12$ c./s.).[4]

Solutions of optically impure I ($[\alpha]_{435}^{25}$ -894° ($CHCl_3$), c 2.5) and II ($[\alpha]_{435}^{26}$ -330° ($CHCl_3$), c 2.4) in freshly distilled mesitylene were separately examined in a 2-dm jacketed polarimeter tube which was maintained at 95.0 ± 0.1° over periods of approximately one half-life (100-155 min.). The average rate constants of racemization, calculated from the first-order law and reported here with 99% confidence limits, were: for I, $k_H = (1.054 \pm 0.019) \times 10^{-4}$ $sec.^{-1}$ (30 readings); for II, $k_D = (0.990 \pm 0.037) \times 10^{-4}$ $sec.^{-1}$ (20 readings). Hence k_H/k_D is approximately 1.06. The effect is undoubtedly real since it is highly improbably (t-test) that the two averages derive from the same set. --Similar results were obtained with different preparations of I and II.

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[3] K. Mislow, Angew. Chem. **70**, 683 (1958).

[4] NMR spectra were measured on a Varian A-60 instrument. Chemical shifts for the spectra (10% solutions in $CDCl_3$) are relative to tetramethylsilane as internal standard.

In order to eliminate the possibility that enol formation had in some way been responsible for the observed isotope effect, the following experiment was performed. A mixture of 0.37 millimole (0.1 g.) of II, 1.1 millimole (0.1 ml.) of n-butyl alcohol and 2.9 ml. of toluene was heated in the 2-dm polarimeter tube for two hours at 95.0± 0.1°. The NMR spectrum[4] of the ketone (after removal of toluene and n-butyl alcohol) was devoid of proton resonance signals in the aliphatic region.

The observed effect is comparable in order of magnitude to several other recently reported kinetic secondary deuterium isotope effects[5]. Although a detailed assessment of the source of the effect must for the present remain a matter of conjecture, an attempt can be made to disentangle some of the factors which could be held to account.

Effects could arise from changes[6] in hybridization of the C-H(D) orbitals which accompany angle bending in the transition state[7]. However, if it is granted that the bond angles in question (at the benzylic carbon atom) are not appreciably deformed, as assumed in our preliminary description of the transition state in related racemizations[2], this source of the effect is of relatively minor importance.

Effects could also arise from changes[6] in nonbonded interaction between hydrogen atoms[8]. There are undoubtedly changes in nonbonded interaction along the reaction

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[5] e.g. A. Streitwieser, Jr. and D. E. Van Sickle, J. Amer. Chem. Soc. **84**, 254 (1962); S. Borčić, M. Nikoletić and D. E. Sunko, Ibid. **84**, 1615 (1962).

[6] The changes referred to are those which accompany the conversion of ground state to transition state of racemization

[7] A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, J. Amer. Chem. Soc. **80**, 2326 (1958).

[8] L. S. Bartell, Tetrahedron Letters No. 6, 13 (1960); L. S. Bartell, J. Am. Chem. Soc. **83**, 3567 (1961).

coordinate of racemization, as has been proposed in closely related situations[9], but these changes are probably slight and it has been recognized that highly crowded systems are required for the direct demonstration of this effect[10]. Furthermore, the direction of the effect conflicts with the naive expectation that I should suffer greater non-bonded interaction in the transition state, and thus should racemize more slowly than II, as a consequence of having the "bulkier" protium atoms.

Finally, "false" isotope effects[11] could possibly account for our data, since the effect is small and the D/H ratio in II is relatively large.

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[9] K. Mislow, S. Hyden and H. Schaefer, J. Am. Chem. Soc. **84** 1449 (1962).

[10] K. Mislow, R. E. O'Brien and H. Schaefer, J. Am. Chem. Soc. **84**, 1940 (1962).

[11] L. Melander, Isotope Effects on Reaction Rates, the Ronald Press Company, New York, N. Y., 1960, p. 96.