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An Unusually Large Secondary Deuterium Isotope Effect. Thermal Trans–Cis Isomerization of *trans*-1-Phenylcyclohexene

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The magnitudes of secondary deuterium isotope effects (SDIE) are generally[1] in the range of $0.9 < k_H/k_D < 1.25$, and are often satisfactorily rationalized by the zero-point energy (ZPE) change on going from reactant to transition state due to C–H rehybridization.[2] We now report a far larger SDIE for the title reaction. Its rationalization on the basis of transition state theory[3] suggests that it more closely resembles a primary isotope effect.

Laser flash photolysis of *cis*-1-phenylcyclohexene (**1**) (direct, 266 nm, or sensitized by thioxanthone, 355 nm) affords its trans isomer **2**,[4] which in heptane exclusively reverts to **1**, $k = 2.1 \times 10^5$ s^{-1} at 300 K. Isotopically substituted **2-*2*-d_1** or **2-*2,6,6*-d_3** (generated similarly from the corresponding cis isomers[5]) both have rates of reversion longer than **2** itself by a factor of 2.0 at room temperature! No previously reported SDIE approaches this magnitude.[6]

Tunnelling contributes modestly to the effect, but we are convinced that it is not dominant. Isotope dependent A factors and possibly a curved Arrhenius plot might be expected as well as a large isotope effect if tunnelling were the key feature. We have measured the temperature dependence of the isomerization rate constant between −20 °C and +73 °C for **2** and **2-*2,6,6*-d_3**. Below 10–15 °C a second-order component corresponding to a reaction of two molecules of **2** (which reaction we believe to be the source of the known[7] low-temperature dimerization) must be subtracted. There is no evidence for curvature in plots of the first-order component (Figure 1), and the activation parameters [**2**, $\log A = 14.1 \pm 0.09$, $E_a = 12.1 \pm 0.12$ kcal/mol; **2-*2,6,6*-d_3**, $\log A = 14.3 \pm 0.11$, $E_a = 12.8 \pm 0.15$ kcal/mol] are not unusual. The A factors are similar to those reported[8] for geometric isomerizations of typical olefins (though at the higher end of the range). Of particular interest regarding tunnelling, the A factors are almost identical with that for *trans*-1-phenyl-2-methylcyclohexene, $\log A = 14.1$, $E_a = 9.9$ kcal/mol. Vinyl H, D, and Me are highly unlikely to give the same A if tunnelling is dominant. However, small to moderate tunnelling corrections to an otherwise "classical" rate would be expected[9] in any reaction in which H(D) motion in the transition state is significant (as must be so in the present case) and are indeed suggested by a plot of isotope effect vs $1/T$: $A_H/A_D = 0.61 \pm .08$ and $E_a^D - E_a^H = 0.77 \pm 0.16$ kcal/mol. That A_H/A_D is somewhat less than unity gives evidence for small to moderate tunnelling.[10]

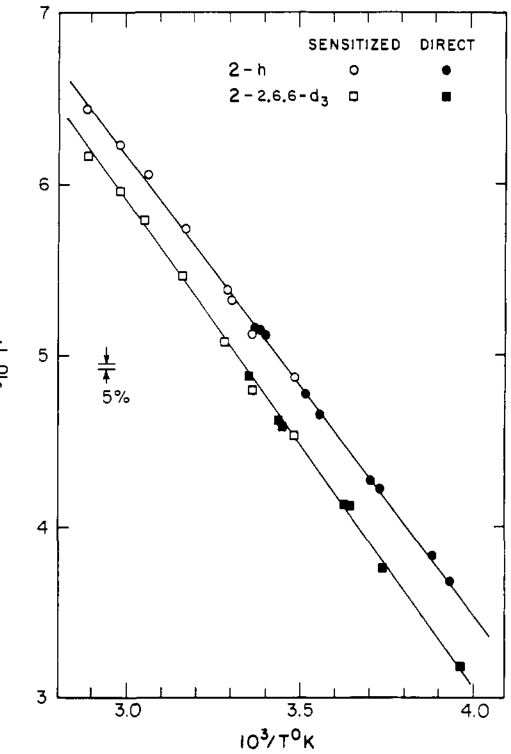

Figure 1. Arrhenius plot for isomerization of **2** and **2-*2,6,6*-d_3** in heptane. Direct irradiation, 266 nm, 0.006 M. Sensitized irradiation (thioxanthone), 355 nm, 0.06 M.

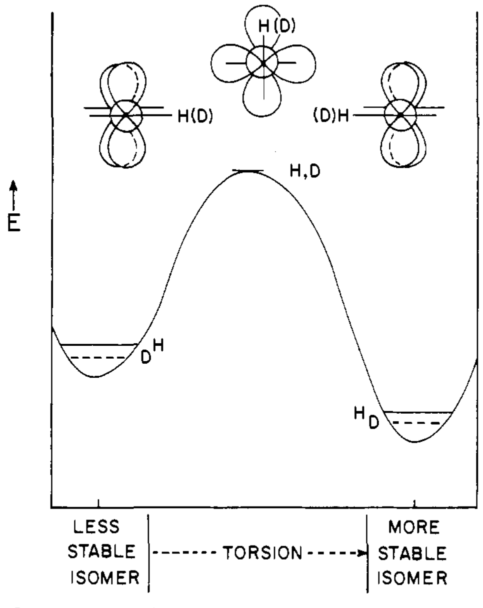

Figure 2. Schematic reaction coordinate plot for geometric isomerization of an olefin showing ZPE corresponding to the C–H (C–D) out-of-plane bend.

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[5] Cristol, S. J.; Davies, D. I. *J. Org. Chem.* **1962**, *27*, 293 and reference therein (**1-*2*-d_1**). Preparation of **1-*2,6,6*-d_3** was by exhaustive deutenation of cyclohexanone followed by addition of PhMgBr and dehydration.

[6] Some large effects are known in solvolysis of β-deuteriated sulfonate esters but are attributed in substantial part to primary effects on elimination of β-H from carbonium ions. See: Stang, P. J.; Summerville, R. *J. Am. Chem. Soc.* **1969**, *91*, 4600. Hargrove, R. J.; Dueber, T. E.; Stang, P. J. *J. Chem. Soc., Chem. Commun.* **1970**, 1614. Seib, R. C.; Shiner, V. J., Jr.; Sendijarevic, V.; Humski, K. *J. Am. Chem. Soc.* **1978**, *100*, 8133. Humski, K.; Sendijarevic, V.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 7722. The largest purely secondary effect to our knowledge is the effect on hyperconjugative stabilization of vinyl cations by β-H(D) at ca. 1.45–1.5, for which also, see: Noyce, D. S.; Schiavelli, M. D. *J. Am. Chem. Soc.* **1968**, *90*, 1023.

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[8] See: Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; John Wiley and Sons: New York, 1976; pp 104ff.

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In geometric isomerization of olefins we consider the reaction coordinate as the C=C torsion, which becomes nonrestorative at the transition state. The isotope dependent mode which is most affected during the reaction is the out-of-plane C–H (C–D) bend (Figure 2). Its frequency in the tranistion state should be very low, behaving analogously to the C–H(D) stretch in H(D) transfers. Assuming an 820-cm^{-1} C–H bending frequency for a trisubstituted alkene[11] and the same factor of 1.36 diminution for C–D bends as for stretches (from the square root of the ratio of the reduced masses) predicts a reduction of the value of about 7 for the primary isotope effect expected for a symmetrical H(D) transfer transition state (without substantial tunnelling) to $7^{(820/2950)} = 1.7$ for the torsional case.[12] For the geometric isomerization transition state of an acyclic olefin, the perpendicularly twisted structure, this should be a reasonable estimate. However, since the vinyl carbons in *trans*-cyclohexene are probably pyramidal[13] and the reactant bending frequency therefore somewhat higher than 820 cm^{-1}, and since there seems to be a modest tunnelling correction, this is a close lower bound. The observation is in excellent accord with this simple model.

The model has been more quantitatively justified by semiempirical molecular orbital calculations. We have examined the prototypical but artificial olefin $M_2C{=}CMH(D)$, where M is a hydrogen of mass 15 (to approximate a methyl group), by MNDO[14] calculations, previous results with which have shown good success in estimating vibrational frequencies[15] as well as deuterium isotope effects on rate.[16] The molecule chosen demonstrates the effect for an acyclic case and avoids the complication of coupling of essential modes with, e.g., internal rotations of the methyl groups were the real case of trimethylethylene used. We find a ZPE contribution to the isotope effect of 1.48 and a total nontunnelling isotope effect of 1.51. In accord with the arguments above, the out-of-plane C–H(D) bending mode of reactant (H, 961 cm^{-1}; D, 812 cm^{-1} calcd) dominates. Other stretches and bends involving the C–H(D) bond are well compensated between reactant and transition state. The imaginary frequency of the activated complex corresponds to the torsion of the M_2C and CMH(D) groups (H, 588i cm^{-1}; D, 481i cm^{-1}) and affords estimated tunnelling corrections to the rate of 1.55 (H) and 1.27 (D) under the usual assumption of a truncated parabolic barrier. The net isotope effect predicted is 1.85, in excellent accord with the observation as well as with the rationalization above.

This is the first SDIE reported for alkene geometric isomerization. It might better be described as "quasiprimary". Just as the entire stretching frequency of a C–H (C–D) oscillator may be "lost" at the transition state for atom transfer, the entire C–H (C–D) out-of-plane bending frequency may be lost in an alkene geometric isomerization. Most importantly, the arguments here presented are not at all unique to the unusual **2**, and large isotope effects should be found for other alkenes as well.

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A New Antitumor Complex: Bis(acetato)bis(imidazole)copper(II)

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The great success of *cis*-diamminedichloroplatinum(II) (*cis*-DDP) in the clinical treatment of human malignancies[1] has stimulated research in the area of so-called second generation platinum compounds[2] and other metal-based antitumor compounds such as titanium,[3] vanadium,[4] gold,[5] germanium,[6] and copper[7] complexes. We have sought new antineoplastic metal complexes based on the following strategy: (i) coordination sphere of the square-planar type, (ii) zero net charge of the complex, and (iii) selection of the moderate leaving ligand. Copper was also chosen as the central metal because of high affinity for nucleic bases of DNA.

Among various copper complexes tested, we found strong antitumor activity in the bis(acetato)bis(imidazole)copper(II) complex, $[Cu(AcO)_2(HIm)_2]$, in which the crystal structure has been clarified.[8] In the 50% inhibition dose (ID_{50})[9] of cell growth using the mouse cancer cell line B16 melanoma,[5] indeed, the cytotoxic effect (20 ng/mL) of $[Cu(AcO)_2(HIm)_2]$ was comparable to that (8 ng/mL) of the excellent therapeutic drug *cis*-DDP and was superior to that (100 ng/mL) of mitomycin C.

Figure 1 shows the ESR spectra of $[Cu(AcO)_2(HIm)_2]$ and the 1:2 Cu(II) complex–deoxyguanosine (dG) systems at 77 K. Both the ESR spectra exhibit a typical Cu(II) hyperfine pattern and are characteristic of pseudo-square-planar Cu(II) system in the local environment of C_{2v} and D_{4h} symmetries.[10,11] In the case

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