

- 46, 238 (1973), and references cited therein; (i) D. Bryce-Smith, A. Gilbert, B. Orger, and H. Tyrrell, *J. Chem. Soc., Chem. Commun.*, 334 (1974); (j) R. M. Bowman, T. R. Chamberlain, C-W Huang, and J. J. McCullough, *J. Amer. Chem. Soc.*, **96**, 692 (1974), and references cited therein.
- (2) (a) H. Leonhardt and A. Weller, *Ber. Bunsenges. Phys. Chem.*, **67**, 791 (1963); (b) for a recent review see A. Lablache-Comblat, *Bull. Chim. Soc. Fr.*, 4791 (1972).
- (3) R. A. Caldwell and L. Smith, *J. Amer. Chem. Soc.*, **96**, 2994 (1974).
- (4) S. Farid, J. C. Doty, and J. L. R. Williams, *J. Chem. Soc., Chem. Commun.*, 711 (1972).
- (5) R. A. Caldwell, *J. Amer. Chem. Soc.*, **95**, 1690 (1973).
- (6) K. Mizuno, C. Pac, and H. Sakurai, *J. Amer. Chem. Soc.*, **96**, 2993 (1974).
- (7) G. Kaupp, *Angew. Chem., Int. Ed. Engl.*, **12**, 765 (1973).
- (8) (a) T. Okada, H. Matsui, H. Oohari, H. Matsumoto, and N. Mataga, *J. Chem. Phys.*, **49**, 4717 (1968); (b) H. Knibbe, K. Röllig, F. P. Schäfer, and A. Weller, *ibid.*, **47**, 1184 (1967), and references cited therein.
- (9) For quenching by 2,3-dimethyl-2-butene steric effects may also be significant.
- (10) From ref 4 and 5,  $k_{isc} = 1.32 \times 10^7 \text{ sec}^{-1}$ ,  $k_{isc} + k_d + k_t = 1.75 \times 10^7 \text{ sec}^{-1}$ ,  $k_F = 7.5 \times 10^9 \text{ l. mol}^{-1} \text{ sec}^{-1}$ , and  $\phi_{C-T} = 0.11$ .
- (11) This analysis leaves little room for enhanced intersystem crossing from an encounter complex preceding the exciplex. cf. (a) N. Orbach, R. Potashnik, and M. Ottolenghi, *J. Phys. Chem.*, **76**, 1133 (1972); (b) Y. Taniguchi and N. Mataga, *Chem. Phys. Lett.*, **13**, 591 (1972).
- (12) L. M. Stephenson and J. I. Brauman, *J. Amer. Chem. Soc.*, **93**, 1988 (1971).
- (13) This simply may be an encounter complex or possess finite stabilization. Emission from termolecular excited state complexes has already been observed. (a) H. Beens and A. Weller, *Chem. Phys. Lett.*, **2**, 140 (1968); (b) H. Ohta and R. A. Caldwell, unpublished results.
- (14) R. A. Caldwell, D. Creed, and H. Ohta, unpublished results.
- (15) Robert A. Welch Foundation Fellow.

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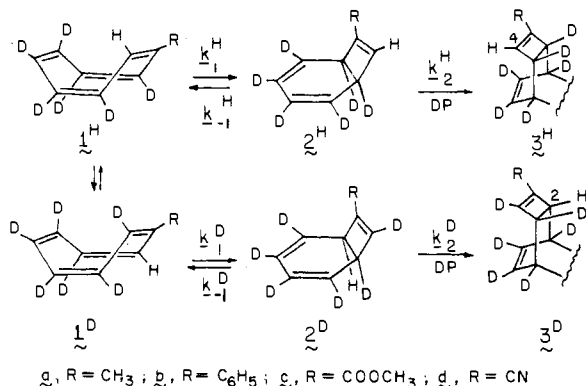
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### The Cyclooctatetraene-Bicyclo[4.2.0]octatriene Equilibrium. A Striking Gradation in Secondary Deuterium Isotope Effects during Diels-Alder Reactions of Monosubstituted Derivatives

Sir:

The kinetically recognizable<sup>1</sup> disrotatory closure of cyclooctatetraene to *cis*-bicyclo[4.2.0]octatriene now serves as the basis for mechanistic discussion of its Diels-Alder reactivity. Empirical substituent effect data on this equilibrium are now appearing, chiefly as the result of investigations aimed primarily at unveiling positional specificity in such cycloadditions.<sup>2</sup> Supplementing these findings, we now report details of a secondary deuterium isotope effect study which reveals for the first time that fractionation factors associated with adduct formation are highly sensitive to the nature of the ring substituent and dienophile (DP).

Polyolefins **1b-d** were prepared in a high state of isotopic



purity by suitable irradiation of the substituted acetylene in benzene-*d*<sub>6</sub><sup>3</sup> while methyl derivative **1a** was obtained by

further transformation of the ester. The direct involvement of **2** requires that production of adducts **3** be controlled by the kinetic expression

$$\frac{d\mathbf{3}^{\text{H}}/dt}{d\mathbf{3}^{\text{D}}/dt} = \frac{[\mathbf{1}^{\text{H}}] k_1^{\text{H}} k_2^{\text{H}} (k_{-1}^{\text{D}} + k_2^{\text{D}}[\text{DP}])}{[\mathbf{1}^{\text{D}}] k_1^{\text{D}} k_2^{\text{D}} (k_{-1}^{\text{H}} + k_2^{\text{H}}[\text{DP}])} \quad (1)$$

which complicated function, herein referred to as case II behavior, has two limiting extremes. If the valence tautomerism occurs rapidly so that the cycloaddition is rate determining ( $k_{-1} \gg k_2[\text{DP}]$ , case I), the rate equation simplifies to

$$\frac{d\mathbf{3}^{\text{H}}/dt}{d\mathbf{3}^{\text{D}}/dt} = \frac{[\mathbf{1}^{\text{H}}] k_1^{\text{H}} k_2^{\text{H}} k_{-1}^{\text{D}}}{[\mathbf{1}^{\text{D}}] k_1^{\text{D}} k_2^{\text{D}} k_{-1}^{\text{H}}} \quad (2)$$

Conversely, when the cycloaddition rate is very fast ( $k_2[\text{DP}] \gg k_{-1}$ , case III), closure to bicyclic form **2** becomes the rate-determining step

$$\frac{d\mathbf{3}^{\text{H}}/dt}{d\mathbf{3}^{\text{D}}/dt} = \frac{[\mathbf{1}^{\text{H}}] k_1^{\text{H}}}{[\mathbf{1}^{\text{D}}] k_1^{\text{D}}} \quad (3)$$

The dienophiles employed were maleic anhydride (MA), tetracyanoethylene (TCNE), and dicyanomaleimide (DCMI). This trio represents a sliding scale of dienophilic capability ranging from the rather unreactive MA through the moderately reactive TCNE to DCMI which sometimes, but not always (*vide infra*), attains limiting case III behavior.<sup>4</sup> Of importance herein, all three undergo cycloaddition to **1** with exclusive capture of the 7-substituted bicyclo[4.2.0]octatrienes (**2**).<sup>5</sup>

Table I summarizes the available data. The cycloadditions were performed using 5–12-fold excess of the dienophile and the products were isolated by a combination of column chromatography and recrystallization. That variations in the amount of DP in this range do not measurably affect the ratios is seen for example in the **1c**-MA reaction where combination at equimolar levels afforded a fractionation factor of 1.50. Temperature and solvent effects are also of little consequence since this same cycloaddition in ethyl acetate at 131°, benzene at 131°, and chlorobenzene at 161° gave results of  $1.49 \pm 0.08$ ,  $1.51 \pm 0.06$ , and  $1.54 \pm 0.07$ , respectively, nor are the spectral determinations biased in a direction which gives excess weighting to the H<sub>4</sub> signal because of some special magnetic factor (*e.g.*, altered transition probability).<sup>6</sup> Finally, a significant departure of the  $\mathbf{1}^{\text{H}} \rightleftharpoons \mathbf{1}^{\text{D}}$  equilibrium from unity does not contribute to the partitioning of protium in the adducts. When **1c** was examined by pmr techniques at -41° (in CDCl<sub>3</sub>),<sup>7</sup> the two signals due to  $\mathbf{1}^{\text{H}}$  ( $\delta$  7.14) and  $\mathbf{1}^{\text{D}}$  (6.07) were equally intense ( $K = 1.0 \pm 0.01$ ).

In the case of the **1b**-DMCI reaction, the limiting case III profile is reached.<sup>1</sup> On this basis, the isotope effect is exclusively  $k_1$  dependent (eq 3) and its magnitude (1.08) ac-

Table I. Deuterium Isotope Effect Data ( $\mathbf{3}^{\text{H}}/\mathbf{3}^{\text{D}}$ )<sup>a</sup>

Compd	Dienophile <sup>b</sup>		
	MA <sup>c</sup>	TCNE <sup>d</sup>	DCMI <sup>e</sup>
<b>1a</b>	$1.26 \pm 0.05$	$1.08 \pm 0.05$	$1.08 \pm 0.04$
<b>1b</b>	$1.30 \pm 0.04$	$1.11 \pm 0.02$	$1.09 \pm 0.03$
<b>1c</b>	$1.55 \pm 0.05$	$1.39 \pm 0.08$	$1.20 \pm 0.03$
<b>1d</b>	$1.55 \pm 0.06$	$1.41 \pm 0.06$	$1.23 \pm 0.08$

<sup>a</sup> Values relate to the intensity ratios of the H<sub>4</sub> and H<sub>2</sub> singlet absorptions ( $H_4/H_2$ ) as determined by repeated integration of expanded scale 100-MHz pmr spectra. <sup>b</sup> All unlabeled counterparts of the 12 adducts have been prepared and fully characterized; mass spectra of the *d*<sub>8</sub> adducts show no loss of deuterium content. <sup>c</sup> Chlorobenzene solvent at reflux (132°). <sup>d</sup> Ethyl acetate solvent at reflux (77°). <sup>e</sup> Benzene solvent at reflux (80°).

cords well with theoretical expectation for a partial change in hybridization of the C<sub>2</sub> carbon from sp<sup>2</sup> to sp<sup>3</sup> in the transition state for disrotatory closure to **2**.<sup>8</sup> The near identity of the other three values in the upper right quadrant of Table I suggests that valence tautomerism is likewise rate limiting in these examples.

The deuterium isotope effects which are evidenced in the cycloaddition of MA to **1a** and **1b** are substantially larger and arise because of reduced dienophilic reactivity which causes the  $k_2$ [DP] and  $k_{-1}$  terms to approach each other in magnitude. The same progression toward case II behavior is witnessed in the DCMI reactions with **1c** and **1d** but for a different reason. In these examples, the diminished concentration gradient of **2c** and **2d** (relative to the methyl and phenyl derivatives) arising from an increase in  $k_{-1}$  is the responsible factor.

The enormous  $k_H/k_D$  values for the **1c**- and **1d**-MA examples, utterly unprecedented in their magnitude, can be understood if the kinetic profile has progressed well into the case I manifold (eq 2). Under these circumstances, a multiplicative isotope effect ( $k_1^H k_{-1}^D / k_1^D k_{-1}^H$ ) obtains. Consequently, limiting case I behavior is merely a preequilibrium situation where **2<sup>H</sup>** and **2<sup>D</sup>** are of necessity in complete equilibrium with each other. Accordingly, these large isotope effects duly reflect the full difference in heats of formation of the isomeric species **2<sup>H</sup>** and **2<sup>D</sup>**. One should recognize that  $k_2$  could be the source of a small fraction of this isotope effect and that it would tend to amplify matters in the observed direction. As concerns eq 2, the assumption has been made that the  $k_2^H$  and  $k_2^D$  terms are essentially identical (thus cancelling) and therefore noncontributory to the isotopic fractionation due to the low level of discrimination anticipated for capture of **2<sup>H</sup>** and **2<sup>D</sup>** by dienophile. To our knowledge, however, experiments designed to assess this specific question remain to be addressed and our assumption must be viewed as presently untested.

To the extent that the isotope effect in case I is indeed wholly derived from an equilibrium isotope effect, then these are unusually large values which reflect the equilibrium isotope effect difference for tetrahedral vs. trigonal deuterium. Notwithstanding, the observed  $K_{eq}$ 's (Table I) are in essential agreement with the best estimates available from consideration of appropriate vibrational frequencies,<sup>9</sup> although this level of magnitude has never been attained in S<sub>N</sub>1 solvolysis reactions.

Thus we have demonstrated that the kinetic deuterium isotope effect at the transition state of a cycloaddition reaction which is preceded by electrocyclic rearrangement is substantially less than that which constitutes equilibrium. The study takes advantage of the correlatability of a predictable mechanistic trend (kinetic order) with a relatively unpredictable but mechanistically sensitive probe (secondary deuterium isotope effects). This method may serve as a simple experimental device to derive useful conclusions concerning the kinetic order of these cycloadditions without resorting to tedious dilatometric rate measurements.<sup>1</sup>

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## References and Notes

- (1) R. Huisgen, F. Mietzsch, G. Boche, and H. Seidl, *Chem. Soc. Spec. Publ.*, No. 19, 3 (1965).
- (2) (a) R. Huisgen, W. E. Konz, and G. E. Gream, *J. Amer. Chem. Soc.*, **92**, 4105 (1970); (b) G. Schröder, G. Kirsch, J. F. M. Oth, R. Huisgen, W. E. Konz, and U. Schnegg, *Chem. Ber.*, **104**, 2405 (1971); (c) R. Huisgen, W. E. Konz, and U. Schnegg, *Angew. Chem.*, **84**, 765 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 715 (1972); J. Gastelger and R. Huisgen,

- Angew. Chem.*, **84**, 766 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 716 (1972); (e) L. A. Paquette, D. R. James, and G. H. Birnberg, *J. Amer. Chem. Soc.*, submitted.
- (3) (a) For a leading reference, consult L. A. Paquette, S. V. Ley, R. H. Meisinger, R. K. Russell, and M. Oku, *J. Amer. Chem. Soc.*, **96**, 5806 (1974). (b) The utilization of benzene-*d*<sub>6</sub> in such reactions is predated: F. A. L. Anet, A. J. R. Bourn, and Y. S. Liu, *ibid.*, **86**, 3576 (1964); L. A. Paquette, M. Oku, W. E. Heyd, and R. H. Meisinger, *ibid.*, **96**, 5815 (1974).
- (4) The highly reactive *N*-phenyltriazolinedione (PTAD) frequently attains case III behavior. However, unlike 2 $\pi$  reactants of lesser reactivity which select only the 7-substituted bicyclo[4.2.0]octatriene, PTAD combines with a greater number of valence tautomers and adds directly to the monocyclic tetraene in certain cases.<sup>2</sup> We have independently established by competition methods that DCMI lies between TCNE and PTAD in its reactivity as a dienophile toward **2**.
- (5) In the case of DCMI, this general mode of positional regioselectivity has also been observed for R = F, OCH<sub>3</sub>, and Br.
- (6) Very careful measurement of signal intensities in the labeled **1c**-MA adduct showed ( $H_4 + H_2$ )/2 >CHC(O)- = 0.51 (theory 0.50), while the unlabeled **1c**-DCMI adduct integrated for ( $H_9 + H_{10}$ )/H<sub>4</sub> = 1.95  $\pm$  0.05 (theory 2.00).
- (7) We thank Dr. S. V. Ley for this experiment.
- (8) In the cyclooctatetraene-MA adduct, the C<sub>4</sub>-H and C<sub>2</sub>-H coupling constants are seen to be 172.1 and 141.6 Hz, respectively, corresponding to 34.4% s (sp<sup>1.90</sup>) and 28.3% s (sp<sup>2.53</sup>) character at these sites: [L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N.Y., 1969, p 345. It follows from these data that the extent of hybridization perturbation in C<sub>4</sub>-H during conversion of **1** to **2** is minimal by comparison.
- (9) Using the carbonyl group as a model, Streitwieser has calculated that the maximum  $\alpha$ -effect arising from changes in the bending force constants during sp<sup>3</sup>  $\rightarrow$  sp<sup>2</sup> rehybridization at the transition state to be 1.40: A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).

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## Stereospecific Intramolecular Epoxide Cleavage by Phenolate Anion. Synthesis of Novel and Biologically Active Cannabinoids

Sir:

As part of a program initiated to further our understanding of the chemical and biological activity of Hashish constituents,<sup>1</sup> we wish to report a stereospecific intramolecular epoxide cleavage by phenolate anion leading to the dihydrobenzofuran,<sup>2</sup> dihydrobenzopyran, and tetrahydrobenzoxepin ring systems. Utilizing this transformation we have effected: (a) the first stereochemically unambiguous synthesis of cannabielsoin<sup>3</sup> (**5**), (b) the preparation of a new biologically potent derivative of  $\Delta^1$ -tetrahydrocannabinol (THC) (**6**); and (c) the synthesis of a novel tetracyclic cannabinoid (**10**) (Scheme I).

Cannabidiol diacetate (**1**), prepared from (-)-cannabidiol<sup>1c,4</sup> (pyridine, acetic anhydride, room temperature, quantitative), gave a mixture of epoxides **2**, **3**, and **4** when allowed to react at room temperature with *m*-chloroperbenzoic acid in chloroform. Gradient elution from Florisil with an ether-petroleum ether solvent system furnished pure diepoxide **4** (40% isolated yield) ( $\delta$  (CCl<sub>4</sub>) 6.73 (s, 2, aromatics), 3.05 (d, 1,  $J = 11$  Hz, C<sub>3</sub>-H), 2.73 (s, 1, C<sub>2</sub>-H, 2 Hz band width at half-height), 2.30 (s, 3, acetate), 2.23 (s, 3, acetate), 2.00, 1.67 (AB, 2  $J = 5$  Hz, C<sub>9</sub>-2H), 1.30 (s, 3, CH<sub>3</sub>), 1.10 (s, 3, CH<sub>3</sub>), 0.88 (t, 3,  $\omega$ -CH<sub>3</sub>)) and a mixture of **2** and **3** (40% isolated yield, in a ratio of 4:1) which shows similar absorptions at 3.10 (d, 1  $J = 11$  Hz, C<sub>3</sub>-H) and 2.80 (s, 1, C<sub>2</sub>-H, 2 Hz band width at half-height). The lack of observable coupling between the C<sub>2</sub>- and C<sub>3</sub>-protons, the presence of significant steric hindrance on the  $\beta$ -face, and the ease of opening these epoxides (see below) make the assignment of an  $\alpha$ -configuration to the endocyclic epoxides<sup>5</sup> in **2** and **4** secure.