Table I. UV Data (λ_{max} ± 1 nm) for Aquo Cobalt Complexes

complex	0.1 M HNO_3	pH 7 buffer	0.1 M NaOH
1	506	526	532
7	522	540	576
11	508	528	534

CM-Sephadex chromatography, the primary-side cyclen-CD conjugate (**4**); in the same way, β-CD monoepoxide (**8**)[7] was converted to the secondary-side cyclen-CD conjugate (**9**). Both compounds gave satisfactory microanalytical, mass spectral, and (albeit complex) NMR data. Cyclen-CD's **4** and **9** were converted to complexes **7** and **11**, respectively, by modification of a literature procedure.[8] Both were obtained as fluffy pink, totally water-soluble solids after lyophilization; each yielded NMR, microanalytical, and mass spectral data consistent with structures **7** and **11**.[9,10]

Kinetic studies were carried out at 25 °C in buffered solution. At pH 7.0, the cyclen–Co(III) complex itself (**1**) (10^{-3} M) does not promote the hydrolysis of *p*-nitrophenyl acetate[11] ("PNP-acetate"; 10^{-4} M), which occurs with a water-catalyzed rate constant of 2.0×10^{-6} s^{-1} at 25 °C. However, addition of primary-side complex **7** (5×10^{-3} M) results in accelerated hydrolysis with a pseudo-first-order rate constant of 1.8×10^{-3} s^{-1} (extrapolated to zero buffer concentration), yielding $k_{complexed}/k_{uncomplexed} = 900$. We note that this represents the largest reported acceleration attributable to CD-induced binding to a metal complex (a 4-fold acceleration has been reported previously[1b]); as expected, the CD-mediated reaction is inhibited competitively by 0.1 M cyclohexanol ($k_1 = 1.9 \times 10^{-4}$ s^{-1}). Because previous studies have found rather small rate differences in reactions catalyzed by primary- and secondary-side derivatives of CD, we were quite surprised to observe that secondary-side complex **11** is an ineffectual catalyst for PNP-acetate hydrolysis. At pH 7.0, complex **11** (10^{-3} M) yields a pseudo-first-order rate constant for PNP-acetate (10^{-4} M) hydrolysis of 7.2×10^{-6} s^{-1}, only 3.6 times faster than the water-catalyzed rate. We postulate that hindered rotation of the cyclen–Co(III) group in complex **11** makes its interaction with bound PNP-acetate less favorable; indeed, it is physically impossible to construct a space-filling model of **11** without some distortion of the cavity.[12]

Complexes **7** and **11** (10^{-3} M) accelerate the hydrolysis of PNP-phosphate (10^{-4} M) at pH 7.0 (25 °C) by factors of 2900- and 3700-fold, respectively, as compared to the uncatalyzed[13] reaction (1.9×10^{-8} s^{-1}). Surprisingly, however, each CD complex is ca. 20 times less effective than is **1** itself in accelerating the PNP-phosphate hydrolysis reaction. In the case of complex **11**, this diminished reactivity can be rationalized as for the ester hydrolysis reaction by freezing the conformation of the Co(III) complex away from the binding site. The rationale for the lessened reactivity of **7** proves more interesting. While the UV spectra of **11** and of **1** are virtually superimposable, the spectrum of **7** indicates a change in its ligand substitution pattern (Table I).[14] It seems likely that an adjacent hydroxymethyl group also coordinates to the cobalt in **7**. Because the proposed mechanism for Co(III)-catalyzed phosphate hydrolysis involves formation of a bidentate phosphacycle intermediate, elimination of one exchangeable coordination site in **7** reduces the activity of the CD-complex even though the PNP acetate result foreshadowed an entropic advantage from precomplexation to the CD binding site. The single exchangeable ligand site on **7** does allow for "monodentate" association with the ester carbonyl group, which can then react either with solvent or with the activated adjacent hydroxyl group to cleave the phosphomonoester bond. Modifications leading to enhanced phosphate hydrolyses may be envisioned, and are the focus of ongoing work.

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(7) Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390. Passage of epoxide **8**, obtained as described in this paper, through an Amberlite MB-3 desalting column affords a salt-free sample as the pentahydrate (by microanalysis) after lyophilization.

(8) Poon, C. K.; Tobe, M. L. *J. Chem. Soc. A* **1968**, 1549. This procedure for the preparation of a cyclam–Co(III) complex was readily adapted for use with the cyclodextrin derivatives by incorporating the modifications shown in Scheme I.

(9) Characterization of **7**: ^1H NMR (D_2O) δ 2.30–4.15 (m, 16 H, azamacrocycle and 42 H, H_2-H_6), 4.90–5.25 (m, 6 H, H_1), 5.28–5.45 (br d, 1 H, H_1); FAB mass spectrum, *m/e* 1347 ($M^+ - H_2O - 3NO_3$). Anal. Calcd for $C_{50}H_{90}CoN_7O_{44}\cdot HNO_3\cdot 6H_2O$: C, 34.53; H, 5.97; N, 6.44. Found: C, 34.80; H, 6.12; N, 6.29.

(10) Characterization of **11**: ^1H NMR (D_2O) δ 2.20–4.40 (m, 16 H, azamacrocycle and 42 H, H_2-H_6), 4.50–5.32 (m, 7 H, H_1); FAB mass spectrum, *m/e* 1347 ($M^+ - 2H_2O - 3NO_3$). Anal. Calcd for $C_{50}H_{92}CoN_7O_{45}\cdot HNO_3\cdot 6H_2O$: C, 34.49; H, 6.08; N, 6.43. Found: C, 34.28; H, 5.93; N, 6.80.

(11) Menger has pointed out that PNP-acetate is an unusually activated ester, reacting more like an anhydride or perhaps a metal-bound ester (Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1987**, *109*, 3145).

(12) While the position at which *manno*-epoxide **8** is attacked by **3** cannot be determined with the PMR spectrum of **9**, analogy to a similar reaction (ref 7) suggests opening at C-3. On the basis of coupling constant data from ref 7, distortion of the substituted sugar residue (and, therefore, of the CD cavity) from the usual $^4C_1$ conformation is indicated.

(13) Extrapolated from the data provided in the following: Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209.

(14) Geometrically induced shifts in the λ_{max}'s of similarly substituted Co(III) complexes have been observed previously: Collman, J. P.; Schneider, P. W. *Inorg. Chem.* **1966**, *5*, 1380.

Diastereotopically Distinct Secondary Deuterium Kinetic Isotope Effects on the Thermal Isomerization of *cis*-Hexatriene to 1,3-Cyclohexadiene

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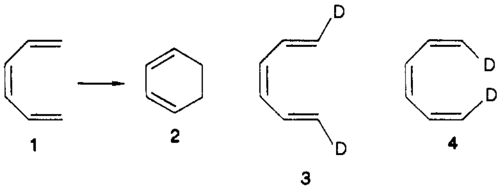
In many pericyclic reactions hydrogens that are equivalent by symmetry in either starting material or product may be diastereotopically related in the transition-state structure and might be associated with different secondary deuterium kinetic isotope effects. These possibilities have not been investigated thoroughly,[1] even though kinetic isotope effects are generally considered one of the most promising means for studying the details of potential surfaces in these reactions.[2,3] We report here a first demonstration



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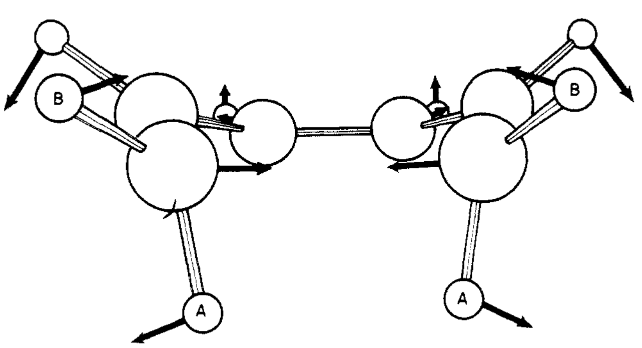

Figure 1. ORTEP drawing of the SCF/6-31G* transition structure. Arrows show motion in the normal mode of imaginary frequency.

of diastereotopically distinct secondary deuterium kinetic isotope effects for a prototypical concerted pericyclic reaction, the thermal isomerization of hexa-1,3*Z*,5-triene (**1**) to 1,3-cyclohexadiene (**2**):[4] these effects, which have been uncovered in both experimental and theoretical work, point toward a more detailed level of understanding of such reactions and transition-state structures.

The stereospecifically deuterium-labeled hexatrienes **3** and **4** were prepared from hex-3*Z*-en-1,5-diyne.[5] Hydroboration using disiamylborane followed by deuterionolysis with CH_3COOD[6] gave the 1*E*,5*E*-$^2H_2$ isomer **3**, while exchange of the acetylenic hydrogens in the enediyne[7] using $NaOD/D_2O$ in di(2-ethoxyethyl) ether, followed by hydroboration and protonolysis, provided the 1*Z*,5*Z*-$^2H_2$ triene **4**. The ^1H NMR spectra of these trienes show the C1,6 prtons in **3** as a doublet (J = 16.7 Hz) at 5.24 ppm, while in **4** the doublet for C1,6 protons (J = 10.1 Hz) is seen at 5.15 ppm.

Competitive thermal isomerizations of hexa-1,3*Z*,5-triene **1** and the deuterium-labeled analogues **3** or **4** were run in the gas phase in a conditioned 1-L Pyrex bulb at 140 °C; analyses of reaction mixtures at given times by GC/MS gave m/e 80/82 data as functions of time, from which [**1**]/[**3**] and [**1**]/[**4**] ratios and relative rate constants were readily derived.[2] The secondary isotope effects (k_H/k_D) for the electrocyclic reactions of **3** and **4** are 1.05 ± 0.03 and 0.88 ± 0.02, respectively. Diastereotopically distinct hydrogens in starting material **1** manifest different secondary deuterium isotope effects on the rate of electrocyclic isomerization.

In order to gain a better understanding of these remarkable secondary isotope effects, ab initio SCF/6-31G* calculations were performed with the program CADPAC[8] on an SCS 40 computer. The triene **1** was found to be nonplanar (C_2 symmetry) in the s-cis,s-cis conformation. The C_s-symmetric transition structure for this disrotatory ring closure was located (Figure 1).[9] Ab initio force constants were computed, then scaled[10] by 0.8, and used to compute vibrational frequencies which in turn gave theoretical secondary isotope effects at 140 °C (no tunneling) of 1.00 for **3** and 0.87 for **4**. Use of Bell's tunneling correction as applied by Saunders[11] increased these to 1.01 for **3** and 0.88 for **4**, in reasonable agreement with experiment.

Diastereotopically distinct secondary deuterium kinetic isotope effects imply diastereoptopically distinct changes in force constants between ground and transition states, which may be associated either with different changes in hybridization or with different changes in nonbonded interactions.[12] From the geometry of **1** and of the transition structure (Figure 1) and the relationship $\lambda_i\lambda_j \cos\theta_{ij} = -1$, one may conclude that the π orbitals at C1 and C6 in the transition state remain of high p character (93%) and that the hybrid orbitals from C to A and B hydrogens experience approximately equal changes in hybridizaton from ground state to transition state. But as the geometry and the normal mode of imaginary frequency (Figure 1) emphasize, A and B hydrogens are associated with very different stereochemical environments in the transition structure, and the A hydrogens may be subject to a substantially greater degree of steric crowding. An increase in intramolecular nonbonding interactions on passage to the transition state may increase force constants for the A hydrogens and give rise to the inverse k_H/k_D effect observed.

Such electrocyclic reactions involve more than a simple rotation of the two metylene groups and a change in hybridization of C1 and C6. The calculated transition structure and the different rates of cyclization shown by **3** and **4** underscore the fact that progress toward C–C bond formation in the transition state is associated with different roles played by the diastereotopically distinct C–H(A) and C–H(B) bonds.

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Diastereotopically Distinct Secondary Deuterium Kinetic Isotope Effects on the Thermal Isomerization of Cyclobutene to Butadiene

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The thermal isomerization of cyclobutene to butadiene, the prototypical electrocyclic reaction first subjected to orbital symmetry based theoretical scrutiny,[1-3] involves a conrotatory process, a distortion from planarity in the carbon skeleton, and sundry rehydridizations; it still attracts substantial calculational attention.[4]

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