pathways for each DCA-sensitized photooxygenation. A number of reported cyanoaromatic-sensitized electron-transfer photooxygenations[28] may prove to be $^1O_2$ reactions upon reinvestigation, using techniques of the sort described here.

Acknowledgment. The authors thank Prof. V. N. Schumaker for use of his single photon counting instrumentation. This work was supported by National Science Foundation Grant CHE80-20140.[38]

Registry No. 1, 591-49-1; **2**, 1674-10-8; **3**, 57-88-5; **4b**, 34310-88-8; **5b,6b**, 16840-37-2; DCA, 1217-45-4; D_2, 7782-39-0; 1-methyl-2-cyclohexenol, 23758-27-2; 2-methylenecyclohexanol, 4065-80-9; 2-methyl-2-cyclohexenol, 20461-30-7; 1-methyl-2-methylenecyclohexanol, 52134-08-4; 1,2-dimethyl-2-cyclohexenol, 51036-24-9; 2,3-dimethyl-2-cyclohexenol, 52134-09-5.

(38) Paper 46: Dobrowolski, D. C.; Foote, C. S. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 720.

Asymmetric Induction Arising from σ/π Interactions

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Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received October 11, 1983. Revised Manuscript Received March 21, 1984*

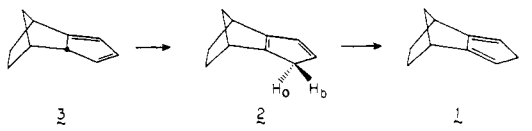
Abstract: Long-range σ/π interactions were unambiguously shown to determine the stereoselectivity of a [1,5]-hydrogen shift. The three isomeric isodicyclopentadienes **1**, **2**, and **3** were prepared, and the cycloadditions and thermal interconversions of these dienes were investigated. A labeling study of the [1,5]-sigmatropic shift transforming **2** to the more stable isomer **1** confirmed the existence of a theoretically predicted interaction of the σ and π orbitals. The preferential migration of the endo hydrogen of **2** by a factor of 6.8 at 125 °C indicated that this effect corresponded to a 1.5-kcal difference in the two diastereotopic transition states.

The transfer of chirality from a chiral center to a reaction site has become an increasing preoccupation of synthetic chemists.[1] For example, significant asymmetric induction can be obtained for the aldol and related condensations by utilization of metal chelates that will permit the manipulation of stereoelectronic factors.[1b] To date these efforts have focused on the exploitation of the diastereotopic transition-state-energy differences arising from differential steric interactions developed along the reaction coordinate. For the most part, efforts to account for stereoselective or stereospecific transformations in terms of electronic influences arising from interaction of the σ and π framework have not been widely pursued.[2,3] We report here examples of asymmetric induction for sigmatropic rearrangements and electrophilic attack arising from molecular orbital interactions.

The classic example for which σ/π interaction has been invoked is the preferential exo attack of electrophiles on norbornene.[2] This explanation has been controversial since two prior explanations had been advanced. Brown suggested that steric hindrance due to the endo C_5 and C_6 hydrogens blocks endo attack.[4] Schleyer invoked the minimization of torsional effects involving the bridgehead C–H bond and the vinylic hydrogen to explain preferential exo attack.[5] The relative importance of these three explanations remains to be convincingly demonstrated.

Fukui originally showed computationally that the exo face of the π bond was asymmetrically extended, thereby providing the means to preferentially stabilize the approach of an electrophile from the exo face.[2c] He attributed this nonequivalent extension of the π system to the mixing of three orbitals: the anti C_7 hydrogen σ bond and/or the methano bridge bonds with the π and σ bonds joining C_2 and C_3 to generate a distorted π orbital, for which an exaggerated representation is shown in Figure 1.[2b] More recently the importance of σ/π mixing for norbornene has been questioned since subsequent computational investigations revealed only slight rehybridization of C_2 and C_3.[6-8] More recently Gleiter has described the σ/π interaction in terms of a hyperconjugative phenomenon entailing minimization of filled shell repulsions, thereby accounting for the disrotatory twisting of the orbitals and slight pyramidization of C_2 and C_3.[7] These findings remain controversial, since Houk has arrived at a similar representation of norbornene by invoking only relief of torsional contributions.[9]

Scheme I



We chose the isodicyclopentadienyl system to evaluate the importance of σ/π electronic interactions to control product stereochemistry. In particular, we focused on the [1,5]-sigmatropic hydrogen migrations that would sequentially convert isodicyclopentadiene **3** via diene **2** to the thermodynamically more stable diene **1** (Scheme I). The critical feature would be whether the chirality of the norbornyl subunit would influence the relative

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(1) (a) Mosher, H. S.; Morrison, J. D. *Science* **1983**, *221*, 1013. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Interscience: New York, 1982; Vol. 13, p 1.

(2) (a) Fukui, K. "Theory of Orientation and Stereoselection"; Springer-Verlag: Heidelberg, 1975. (b) Fukui, K.; Fujimoto, H.; Inagaki, S. *J. Am. Chem. Soc.* **1976**, *98*, 4054. (c) Inagaki, S.; Fukui, F. *Chem. Lett.* **1974**, 509.

(3) (a) Liotta, C. L. *Tetrahedron Lett.* **1975**, 519, 523. (b) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703.

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(5) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1967**, *89*, 701.

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(7) (a) Spanget-Larsen, J.; Gleiter, R. *Tetrahedron Lett.* **1982**, 2435. (b) Spanget-Larsen, J.; Gleiter, R. *Tetrahedron* **1983**, *39*, 3345.

(8) (a) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan, N. G.; Domelsmith, L. N.; Rozeboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482. (b) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. *Ibid.* **1981**, *103*, 2436.

(9) (a) Caramella, P.; Rondan, N. G.; Padden-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. (b) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Mareda, J.; Mueller, P. H.; Houk, K. N. *Ibid.* **1982**, *104*, 4974. (c) Houk, K. N.; Rondan, N. G.; Brown, F. K.; Jorgensen, W. L.; Madura, J. D.; Spellmeyer, D. C. *Ibid.* **1983**, *105*, 5980.

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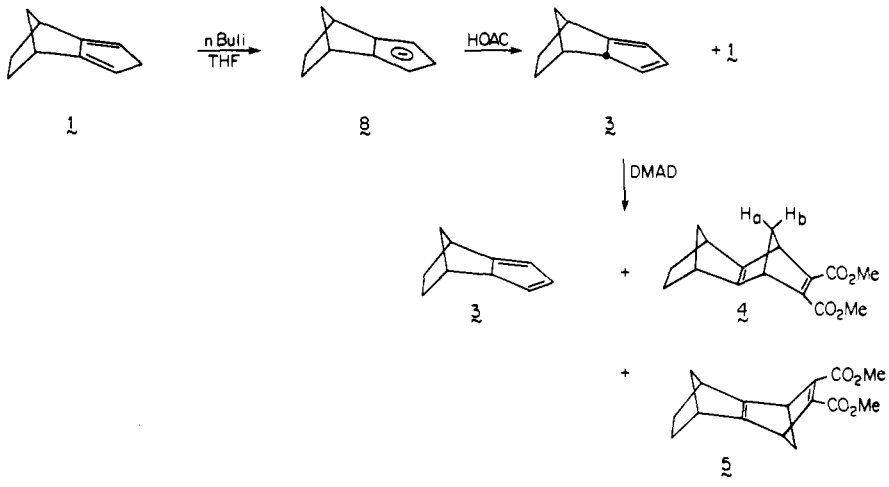
Scheme II



migratory aptitude of the endo (H_a) and exo (H_b) hydrogens of **2**. Inspection of molecular models reveals that the diene moiety is well removed from the bicyclic component; therefore steric and torsional influences should not be significant. Since the rearrangement would be a unimolecular gas-phase reaction, no perturbation in reaction course due to preferential solvation or counterion influence would be involved.[10]

We partially optimized the geometry of **2** by CNDO calculations,[11] before examining the HOMO of diene **2** by EHT[12] and ab initio (STO-3G) calculations.[13] A contour plot revealed that the electron density was slightly greater on the exo face of the C_2C_6 double bond, just as for norbornene. The fourth contour line of Figure 2 reveals this nonequivalent extension of this double bond. The lobes of the C_3C_4 double bond were distorted in the opposite sense, resulting in more electron density on the endo face. As the plot indicates (Figure 3), the orbital on C_4 was markedly extended, whereas the C_3 orbital was almost unperturbed. The fifth contour best reveals this difference in electron density. Thus, on the basis of these calculations, H_a, the endo hydrogen of **2**, was expected to preferentially migrate, because the more diffuse endo lobe of C_4 would permit earlier bonding to the migrating hydrogen, thereby lowering the transition-state energy.

The relative transition-state energies for the sigmatropic shift of the endo vs. exo hydrogen of **2** were calculated for the conversion of **2** to **1** using the STO-3G basis set. No attempt was made to optimize geometry. In each case the migrating hydrogen was oriented at an angle 74.4° out of the plane of the planar cyclopentadienyl ring and located 1.34 Å from both C_4 and C_5. The remaining hydrogens at C_4 and C_5 were bent 29.4° out of the plane of the cyclopentadienyl ring. The small 1.2-kcal difference in transition-state energies in favor of the migration of the endo hydrogen suggested that the transformation of **2** to **1** may be stereoselective for H_a.

At the time this work was undertaken, only tricyclo-[5.2.1.$0^{2,6}$]deca-2,5-diene, 3-isodicyclopentadiene (**1**), was known.[14,15] The reports by Alder and Sugimoto that **1** underwent an unanticipated stereospecific 2 + 4 cycloaddition from the endo face prompted suggestions that steric attraction was responsible for the stereospecificity.[14,16] Further investigations by Paquette confirmed that **1** reacted only from the endo face with a variety

Figure 1. Schematic representation of the origin of the nonequivalent π-orbital extension of norbornene.

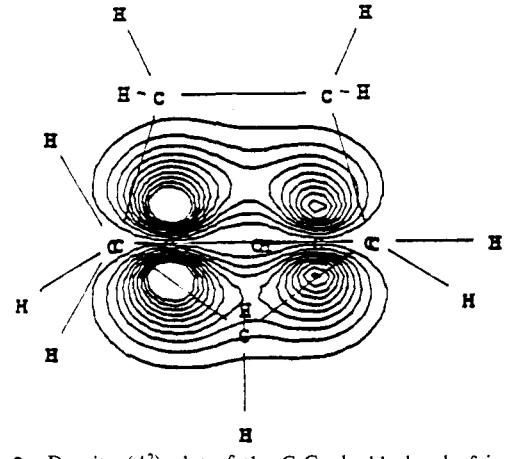


Figure 2. Density (ψ^2) plot of the C_2C_6 double bond of isodicyclopentadiene **2** with contour levels of 0.01–0.10 e/Au^3 in increments of 0.01.

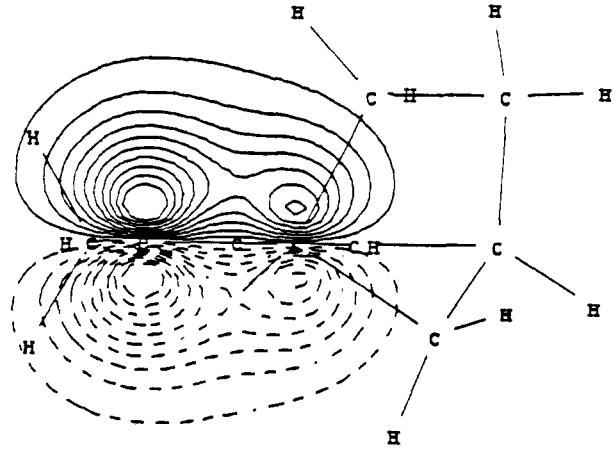
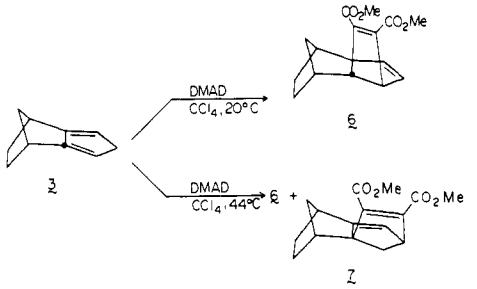


Figure 3. Wave-function (ψ) plot of the C_3C_4 double bond of isodicyclopentadiene **2** with contour lines of 0.02–0.2 Au in increments of 0.02.

(10) Analogous efforts to demonstrate frontier orbital control of the stereochemistry of the S_N2' reaction were greatly hampered by these factors.
(11) Pople, J. A.; Santry, D. P.; Segal, G. A. *J. Chem. Phys.* **1963**, *43*, 5129.
(12) Hoffmann, R. *J. Chem. Phys.* **1963**, *39*, 1397.
(13) Computations utilized the GAUSSIAN70 prgram: Hehre, W. J.; Ditchfield, R.; Newton, M. D.; Pople, J. A. *QCPE* **1973**, *11*, 236. (b) STO-3G basis set: Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657.
(14) Alder, K.; Flock, F. H.; Janssen, P. *Chem. Ber.* **1956**, *89*, 2689.
(15) Katz, T. J.; Rosenberger, M.; O'Hara, R. K. *J. Am. Chem. Soc.* **1964**, *86*, 249.
(16) Sugimoto, T.; Kobuke, Y.; Furukawa, J. *J. Org. Chem.* **1976**, *41*, 1457.

Scheme III



of dienophiles to generate the *syn*-sesquinorbornene skeleton.[17a,b] More recently Bartlett, in a report which appeared after completion of this work, found that **1** reacted with maleic anhydride to give a 2:1 mixture of the *syn*- and *anti*-sesquinorbornene derivatives.[18] Gleiter and Paquette have invoked σ/π interactions entailing subjacent orbital control to account for the preferential cycloadditon of dienophiles to the endo face of **1**.[17b,d] The repulsive hyperconjugative interaction of ψ_s, the symmetric occupied orbital of the butadiene fragment, with the low-lying σ orbitals of the methano bridge would induce the π orbitals to undergo a disrotatory rotation. When viewed from the exo face, C_2 and C_6 rotate outward whereas C_3 and C_5 rotate inward. An endo approach of the dienophile to this distorted π ensemble would minimize filled shell repulsions.

We found that treatment of **1** with *n*-butyllithium in THF followed by an acetic acid quench at 0 °C generated a 1.2:1 mixture of the hitherto unknown isomeric isodicyclopentadiene **3** and diene **1**.[19] Diene **3** was purified by titrating the mixture with dimethyl acetylenedicarboxylate (DMAD) at 20 °C until all of **1** underwent cycloaddition and then transferring the residual **3** on a vacuum line (Scheme II). HPLC analysis showed two adducts, in a ratio of 16:1. The major one, **4**, was identical with the *syn*-sesquinorbornadiene product reported by Bartlett for this cycloaddition.[20] The minor product was the corresponding *anti*-sesquinorbornadiene **5**; ^{13}C NMR clearly established the C_{2v} symmetry of **4** and **5**. In the ^1H NMR spectra of adduct **4**, the hydrogens of the cyclopentadiene moiety of **1** are well resolved.

Diene **3** is stable and when heated at 56 °C in CCl_4 formed a mixture of four dimers in addition to small amounts of **1**. When **3** was pyrolyzed at 125 °C by using a N_2 stream to carry **3** through a hot Pyrex tube and the effluents were trapped at −75 °C, the sole product was diene **1**. Diene **3** reacted with DMAD in CCl_4 at 20 °C over 24 h to form a single Diels–Alder adduct **6** (Scheme III). The exo orientation of **6** was tentatively assigned on the basis of the ^{13}C NMR spectrum;[21] subsequently Bartlett has assigned a similarly oriented structure to the maleic anhydride adduct of **3** on the basis of X-ray crystallographic data.[22]

When the above reaction was run at 44 °C, a mixture of **6** and **7** was formed. Adduct **7** was a 1:1 Diels–Alder adduct of diene **2** and DMAD. The orientation of **7** could not be assigned from the ^1H or ^{13}C NMR spectrum. Paquette and Bartlett later reported that X-ray crystallography of adducts of **2** revealed that cycloaddition occurred from the exo face.[20,23] By analogy, the same orientation is assumed for **7**. These investigators had prepared adducts of **2** by heating solutions of diene **1** at 170 °C with dienophiles of moderate reactivity, since under these conditions a thermal equilibrium was established between **1** and the more reactive isomer **2**. Comparison of the reaction conditions required to generate **2** underscores the difference in activation barriers for the [1,5]-hydrogen migration converting **1** into **2** vs. **3** into **2**. Despite the ease with which **2** is further isomerized to **1**,[24] we observed no formation of adduct **4** or **5**, reflecting the high propensity of **2** to undergo cycloadditions with DMAD. This reactivity is consistent with Huisgen's findings that norbornenyl double bonds are particularly prone to cycloadditions, presumably owing to Fukui's proposed nonequivalent orbital extension.[2,25]

To determine the relative migratory aptitude of the endo vs. exo hydrogens of the intermediary **2** during the transformation of **3** to **1**, we prepared monodeuterated **3a** and trideuterated **3b**. In the preparation of **3a**, HOAc-d_1 was substituted for HOAc in Scheme II; the resulting 1.6:1 mixture of **1a** and **3a** was separated as previously described. The synthesis of trideuterated **3b** entailed exhaustive exchange of **1** with alkaline D_2O/HMPA followed by sequential treatment with *n*-BuLi, HOAc, and DMAD. The deuterium content of **3a** and **3b** was determined by converting a portion of each to the DMAD adduct, which, by mass spectrometry, contained 0.96 and 3.0 deuteriums, respectively.

Gas-phase pyrolysis of **3a** at 126 °C followed by treatment with DMAD generated adduct **4a**, which after HPLC purification contained 0.96 deuterium by mass spectral analysis (Scheme IV). By ^2H NMR the deuterium was shown to be distributed in a 15:1 ratio between C_3, the bridgehead carbon, and C_{11}, the newly formed methano bridge. These results reveal that ~94% of the deuterium label in the thermal product must reside at C_3 of monodeuterated **1**-d_1. Thus 94% of the time the endo hydrogen (H_a) of the intermediary monodeuterated **2a** underwent the sigmatropic migration. Thus the relative migratory aptitude ($k_{H(endo)}/k_{D(exo)}$) is 15 ± 1.

An isotope effect of 15 for a [1,5]-sigmatropic hydrogen migration would be most unusual.[26] In view of the low transition-state energy for conversion of **2** to **1**, the isomerization of 5-methylcyclopentadiene to 1-methylcyclopentadiene ($\Delta H^{\ddagger}$ = 19.3 kcal[27]) was chosen as a model. McLean had reported the temperature dependence of k_H/k_D for this isomerization.[28] An extrapolation of his data predicted that the isotope effect would be 2.05 at 122 °C. To establish that the isotope effect for the sigmatropic rearrangement of the isodicyclopentadienes was typical, we determined k_H/k_D for the isomerization of **3** to **2** at 122 °C to be 1.92 ± 0.07. With the isotope effect for the isodicyclopentadienyl system established as typical, the huge discrepancy between the observed value of 15 for the isomerization of **2a** to **1**-d_1 and the normal value of ~2 for the conversion of **3** to **2** suggested that the value of 15 was due to two effects acting in concert. In this instance the isotope effect was being reenforced by the postulated positional effect favoring the migration of the endo hydrogen atom.

To confirm this analysis, we pyrolyzed the trideuterated diene **3b** at 121 °C as before; the product **1b** was trapped with DMAD and analyzed (Scheme V). By mass spectrometry the deuterium content of the isolated adduct **4b** was 3.0 D; by ^1H NMR 0.75 of the hydrogen label was at C_3, the bridgehead of the trideuterated

(17) (a) Paquette, L. A.; Carr, R. V. C.; Bohm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1980**, *102*, 1186. (b) Bohm, M. C.; Carr, R. V. C.; Gleiter, R.; Paquette, L. A. *Ibid.* **1980**, *102*, 7218. (c) Paquette, L. A.; Carr, R. V. C.; Charumilind, P.; Blount, J. F. *J. Org. Chem.* **1980**, *45*, 4922. (d) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328.

(18) Watson, W. H.; Galloy, J.; Bartlett, P. D.; Roof, A. A. M. *J. Am. Chem. Soc.* **1981**, *103*, 2022.

(19) Recently a similar synthesis of a mixture of **1** and **3** was reported. Bartlett, P. D.; Wu, C. *J. Am. Chem. Soc.* **1983**, *105*, 100.

(20) Subramanyam, R.; Bartlett, P. D.; Iglesias, G. Y. M.; Watson, W. H.; Galloy, J. *J. Org. Chem.* **1982**, *47*, 4491.

(21) A molecular model of **6** revealed that the environment of the two carbons comprising the exo-oriented vinyl bridge would be similar but that one of the two carbons of the endo-oriented vinyl bridge would be sterically congested and experience γ shielding. Analysis of the ^{13}C spectrum indicated that the two sp^2 carbons bearing the carbomethoxy groups were nearly equivalent whereas the carbons comprising the unsubstituted vinyl bridge were nonequivalent. This observation suggested that the unsubstituted vinyl bridge carbons must experience dissimilar environments. Therefore the DMAD cycloaddition occurred from the exo face of **3**.

(22) We thank Professor Bartlett for providing this information.

(23) Paquette, L. A.; Williams, R. V.; Carr, R. V. C.; Charumilind, P.; Blount, J. F. *J. Org. Chem.* **1982**, *47*, 4566.

(24) Bartlett reported that **2** could be prepared at 0 °C in solution but immediately isomerized to **1** upon warming to 20 °C.[20]

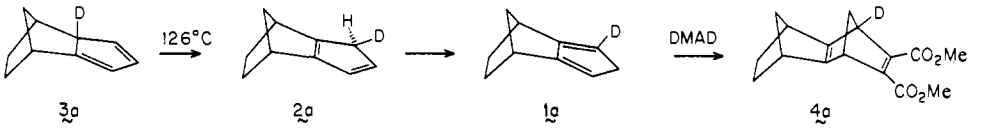
(25) (a) Huisgen, R.; Ooms, P. H. J.; Mingin, M.; Allinger, N. L. *J. Am. Chem. Soc.* **1980**, *102*, 3951. (b) Huisgen, R. *Pure Appl. Chem.* **1981**, *53*, 171.

(26) For recent reviews of [1,5] migrations, see: (a) Mironov, V. A.; Fedorovich, A. D.; Akrem, A. A. *Russ. Chem. Rev.* (*Engl. Transl.*) **1981**, *50*, 666. (b) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.

(27) McLean, S.; Webster, C. J.; Rutherford, J. D. *Can. J. Chem.* **1969**, *47*, 1555.

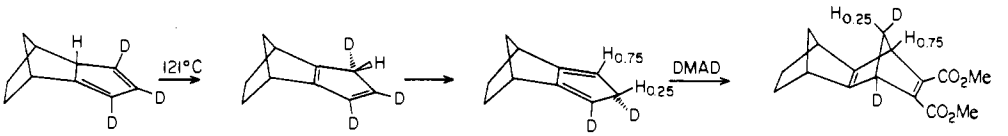
(28) $k_H = 7.49 \times 10^{10} e^{(-19930/RT)}$; $k_D = 7.58 \times 10^{11} e^{(-22350/RT)}$.

Scheme IV



3a 2a 1a 4a

Scheme V



3b 2b 1b 4b

adduct **4b**, and the remaining 0.25 was present at the methano bridge. Thus for diene **2b** the deuterium preferentially migrated ($k_{D(endo)}/k_{H(exo)} = 3 \pm 0.05$).

The hydrogens of C_{11}, the newly formed methano bridge of the undeuterated adduct **4**, resonated at δ 2.05 and 2.4. However, the hydrogen present in the corresponding methano bridge of the trideuterated adduct **4b** resonated at δ 2.05; no signal was observed at δ 2.4. The fact that only the δ 2.05 signal was seen meant that no scrambling of the label had occurred during the formation and trapping of **1b**, thereby establishing that H_a and H_b of diene **2** maintain their orientation during the thermal rearrangement. Furthermore, the resonances of the hydrogens of C_{11} of adduct **4** can be assigned, since the C_6 hydrogen label of diene **1b** appeared only at δ 2.05 and not at δ 2.4 in adduct **4b**. Thus the syn hydrogen (H_a) of **4** resonates at δ 2.05 and the anti one (H_b) at δ 2.4. This assignment was later confirmed by Bartlett using a lanthanide shift reagent to assign the corresponding hydrogens of the analogous adduct formed from cycloaddition of **1** with maleic anhydride.[19]

The dependence of migratory aptitude of a hydrogen vs. a deuterium on the orientation of these two hydrogen isotopes in **2** clearly indicates the involvement of two factors: an isotope effect (k_H/k_D) and an orientational effect (k_{endo}/k_{exo}). The contribution of each can be calculated from the results obtained from **3a** and **3b** as outlined below, if secondary deuterium isotope effects are ignored.

From diene **3a**

$$k_{H(endo)}/k_{D(exo)} = 15 = (k_H/k_D)(k_{endo}/k_{exo})$$

From diene **3b**

$$k_{D(endo)}/k_{H(exo)} = 3 = (k_D/k_H)(k_{endo}/k_{exo})$$

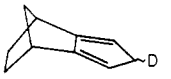
Given two equations and two unknowns, algebraic manipulations result in the following solutions:

$$k_H/k_D = 2.2 \pm 0.4$$

$$k_{endo}/k_{exo} = 6.8 \pm 1.2$$

At 126 °C a factor of 6.8 corresponds to a diastereotopic transition-state-energy difference of 1.5 kcal, reflecting the positional effect arising from the exo vs. endo orientation of the two hydrogens of diene **2**.

These results are different from the study Bartlett reported concerning the scrambling of the deuterium label of **1c** upon



1c

heating **1c** to 100 °C in CCl_4.[19] In that study aliquots were withdrawn to determine the deuterium label distribution over C_3, C_4, and C_5 of **1** as a function of time. The rate constants were deduced by computer modeling, and an isotope effect was calculated to be 6.5. The critical assumption for their analysis was that the migratory aptitudes of the endo and exo hydrogens of **2** and **1** were the same. Our finding of a pronounced bias for migration of the endo hydrogens means that their conclusions should be reinterpreted.[29]

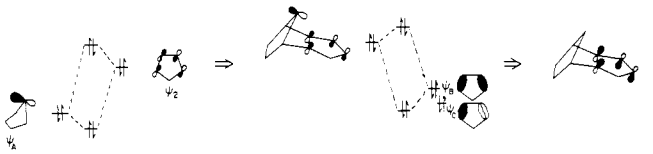


Figure 4. Schematic representation of the origin of the nonequivalent orbital extension of the HOMO of isodicyclopentadiene **2**.

The enhanced migratory aptitude of the endo hydrogen (H_a) of **2** can be most easily explained by an electronic perturbation induced by interaction of the σ and π molecular orbitals. The perturbation of the π system can arise from either a hyperconjugative interaction of the butadiene moiety of **2** with the norbornyl σ framework or from mixing of these orbitals.[30] The hyperconjugative interaction would induce a twisting of the C_4 π orbital analogous to that observed by Paquette and Gleiter for diene **1**.[17b,d] In this instance the twisting of the π orbital would result in the endo lobe being directed toward H_a, the endo hydrogen thereby enhancing the migratory aptitude.

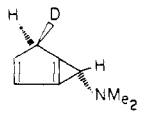
The perturbation of **2** induced by σ/π mixing can be described in frontier orbital terms by dissecting **2** into cyclopentadienyl and cyclopentyl components. By analogy to norbornene, the interacting orbitals would be ψ_2, the HOMO of the cyclopentadienyl fragment; either ψ_B or ψ_C, the highest lying σ orbital of the cyclopentadienyl fragment; and ψ_A, the carbon–hydrogen bond of the cyclopentyl fragment. The out-of-phase interaction of ψ_2 with ψ_A perturbs the π orbital as shown in Figure 4. The resulting perturbed orbital mixes in phase with the highest lying σ orbital of the cyclopentadienyl ring, i.e., either ψ_B or ψ_C. From EHT calculations on this fragment, the symmetric orbital, ψ_B, lies 0.15 eV above the nonsymmetric counterpart. Consequently, according to frontier orbital considerations, the perturbed π orbital would mix more strongly with ψ_B, leading to higher electron density at C_2 and C_6 on the exo face and higher density at C_3 and C_4 on the endo face of diene **2**. This resulting π molecular orbital also would suggest that the migration of the endo hydrogen of **2** would be favored.

The isodicyclopentadienyl system is not the first instance for which deuterium rather than hydrogen preferentially underwent a [1,5] migration. During a mechanistic investigation of bicyclo[3.1.0]hexatriene, a similar preference for deuterium migration was discovered.[31] In that study an intermediary *anti*-4-deuterio-6-(dimethylamino)bicyclo[3.1.0]hexa-1^{1,5},2-diene (**9**) was transformed into *anti*-5-deuterio-6-(dimethylamino)bicyclo-[3.1.0]hexa-1,3-diene (**10**). Product analysis revealed that for that

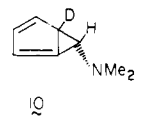
(29) Recently in a related experiment, Paquette attempted unsuccessfully to prepare diene **1**, stereospecifically bis silylated at C_4, with the intent of inducing a [1,5]-silylatropic migration in order to ascertain the relative migratory aptitudes of the endo and exo substituents. Paquette, L. A.; Charumilind, P.; Gallucci, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 7364.

(30) Computational studies to delineate the relative importance of these factors are in progress.

(31) Washburn, W. N.; Zahler, R.; Chen, I. *J. Am. Chem. Soc.* **1978**, *100*, 5863.



rearrangement k_D/k_H was >4 at −75 °C. This value corresponds



to a ~1.2-kcal difference in diastereotopic transition-state energies. A similar nonequivalent extension of the π molecular orbital due to interaction with the asymmetric σ framework was invoked to account for the preferential migration of the hydrogen isotope anti to the dimethylamino group.

In conclusion, these results demonstrate the ability of a remote norbornenyl moiety to determine the relative energies of diastereotopic transition states. In this instance the probe, being a hydrogen atom moving across the face of a π system, would induce the minimum perturbation possible. Consequently, the results of this study, indicating a 1.5-kcal difference in diastereotopic transition-state energies, must reflect the electronic bias for migration of the endo hydrogen atom due to an unsymmetric extension of the π molecular orbital. These findings agree with theoretical predictions based either on frontier orbital considerations or on ab initio calculations. Moreover, at least one other system composed of a cyclopentadienyl ring fused to an asymmetric unit has demonstrated similar selectivity for [1,5] migrations. This electronically induced selectivity favoring interaction with the system from the endo face operated even in solution and influenced the course of electrophilic attack on the isodicyclopentadienyl anion.[32] Since σ/π interactions of this type are not limited to the norbornyl system, the intriguing question is whether these considerations are important in determining the stereoselectivity of other reactions proceeding via rigid geometries imposed either by covalent bonding or by chelation.

Experimental Section

^{1}H NMR spectra were recorded on either a Varian EM-390 or a UCB 180-MHz FT superconducting spectrometer; ^{2}H NMR spectra were recorded on the UCB 180 instrument. ^{13}C NMR spectra were measured at either 25.14 MHz on a Nicolet TT-23 spectrometer or at 45.28 MHz on the UCB 180 instrument. UV spectra were recorded on a Cary 118 spectrometer; IR spectra were obtained on a Perkin-Elmer Model 297 spectrometer. Mass spectra were run on either an Atlas MS-12 or a Consolidated 120B mass spectrometer. All analytical GLPC work was done with a Perkin-Elmer 3920 gas chromatograph equipped with a flame ionization detector and columns packed with 5% SE-30 on Chromosorb G. An Aerograph Autoprep A-7000 was used for preparative work. All analytical and preparative HPLC work was run on a Waters Model 6000 A liquid chromatograph equipped with a Waters 400 absorbance detector monitoring at 254 nm, with μPorisil-packed columns and methylene chloride as the solvent. THF and HMPA were distilled from Na. The isodicyclopentadiene **1** was prepared as reported.[14,15]

Reaction of Isodicyclopentadiene 1 with DMAD. To a solution containing 1.6 mmol of diene **1** in 1 mL of CCl_4 at 35 °C under N_2 was added 2.0 mmol of DMAD in portions over 2 h. After volatiles were removed at 0.05 torr, HPLC analysis revealed three products, adducts **4** and **5** and an air-oxidation product of **4**, present in the ratio of 16:1:1.

Adduct **4**: IR (CCl_4) 2955, 2950, 1718 cm^{-1}; UV (CH_3CN) 245, 209 nm; ^{1}H NMR (CCl_4) δ 3.6 (s, 8 H), 2.92 (s, 2 H), 2.4 (dt, 1 H), 2.05 (dt, 1 H), 1.4 (m, 3 H), 1.1 (dt, 1 H), 0.5 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.6, 158.4, 150.0, 69.9, 51.8, 51.6, 48.2, 42.6, 22.0; mass spectrum, *m/e* 274, 246, 214; HRMS 274.1202; calcd for $C_{16}H_{18}O_4$ 274.1205.

Adduct **5**: IR (CCl_4) 2950, 1720 cm^{-1}; UV (CH_3CN) 254, 211 nm; ^{1}H NMR (CCl_4) δ 3.6 (s, 8 H), 3.05 (d, 2 H), 2.4 (d, 1 H), 2.0 (d, 1 H), 1.8–0.8 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 160.5, 153.5, 79.3, 52.0, 51.2, 50.4, 43.3, 25.7; mass spectrum, *m/e* 274, 246, 214; HRMS 274.1213; calcd for $C_{16}H_{18}O_4$ 274.1205.

Preparation of *endo*-Tricyclo[5.2.1.0^{2,6}]deca-2,4-diene (3). To a stirred solution of 3.13 g (23.7 mmol) of **1**, a trace of triphenylmethane, and 30 mL of THF under N_2 at 0 °C was slowly added sufficient 2.2 M *n*-BuLi/hexane solution to generate a red hue. The solution was warmed to 20 °C, stirred for 15 min, and slowly transferred by syringe to a stirred 0 °C solution of 3 mL of HOAc in 15 mL of THF. The quenched solution was poured into H_2O and extracted three times with Et_2O. The combined organic extracts were washed three times with with H_2O, dried over $MgSO_4$, and concentrated under vacuum. Care was taken to minimize the exposure of **1** and **3** to air. Dienes **1** and **3** could be stored indefinitely in CCl_4 under N_2 at −75 °C. By ^{1}H NMR analysis **1** and **3** were present in a ratio of 1:1.2. The solution was titrated at 20 °C with DMAD, with ^{1}H NMR used to determine when all **1** was consumed. The volatiles were transferred on a vacuum line at 0.05 torr to remove **3** from **4** and **5**. Diene **3**: ^{1}H NMR (CCl_4) δ 6.5 (d, 1 H), 5.9 (d, 2 H), 3.0 (s, 2 H), 2.55 (s, 1 H), 1.8–0.9 (m, 6 H).

Characterization of 3. Diene **3** was exhaustively reduced in EtOH over 5% Pd/C, generating a single product, which was identical by GLPC, ^{1}H NMR, and ^{13}C NMR with tetrahydrodicyclopentadiene formed from reduction of dicyclopentadiene. ^{13}C NMR ($CDCl_3$) δ 45.7, 43.4, 41.6, 28.9, 26.9, 23.1.

Diene **3** was unchanged upon standing for 3.5 h at 20 °C in degassed CCl_4. Heating a 0.1 M solution of **3** in N_2-purged CCl_4 for 19 h at 56 °C caused complete consumption of **3**. The major products by GC/MS were four dimers. Careful ^{1}H NMR analysis of the volatile fraction, after it was separated from the dimers by vacuum-line transfer, revealed a small amount of diene **1**.

Preparation of 6. A CCl_4 solution 0.1 M in diene **3** and 0.2 M in DMAD was allowed to stand at 20 °C under N_2 for 48 h. After removal of the volatiles on a vacuum line, HPLC analysis revealed only one adduct, **6**. Adduct **6**: IR (CCl_4) 2950, 1715 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.85 (d, 1 H), 6.4 (q, 1 H), 4.04 (d, 1 H), 3.65 (s, 3 H), 3.6 (s, 3 H), 2.82 (s, 2 H), 2.4 (s, 1 H), 1.8–1.1 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 159.2, 158.8, 144.4, 132.9, 93.3, 73.5, 54.6, 51.7, 51.6, 47.1, 42.9, 36.5, 28.3, 21.8; mass spectrum, *m/e* 274, 215, 187, 155; HRMS 274.1200; calcd for $C_{16}H_{18}O_4$ 274.1205.

Preparation of 7. A solution containing 1 mmol of **3** and 2 mmol of DMAD in 10 mL of CCl_4 was heated at 40 °C under N_2 for 19 h. ^{1}H NMR and HPLC analyses revealed two adducts, **6** and **7**, in a 1.9:1 mixture, which was separated by HPLC. Adduct **7**: IR (CCl_4) 2950, 1720 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.0 (d, 1 H), 3.85 (m, 1 H), 3.75 (s, 3 H), 3.7 (s, 3 H), 2.85 (m, 2 H), 2.05 (s, 2 H), 2.0–1.3 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 167.0, 164.4, 155.1, 148.2, 122.4, 75.3, 73.6, 53.2, 51.7, 51.5, 43.5, 37.6, 30.7, 23.8; mass spectrum, *m/e* 274, 242, 215, 187; HRMS 274.1205; calcd for $C_{16}H_{18}O_4$ 274.1205.

Diene **3a** was converted to adduct **7a** monodeuterated at C_{11} as described above. The ^{1}H NMR of **7a** was identical with that of **7** except that the singlet at δ 2.05 integrated for only 1 H. The ^{1}H NMR spectrum of adduct **7b**, prepared as above from trideuterated diene **3b**, differed from the spectrum of **7** in that the peaks centered at δ 6.0 and 3.85 were absent and the peak at δ 2.05 integrated for only 1 H.

Gas-Phase Pyrolysis of 3. Nitrogen flowing at 28 mL/min was passed over a stirred solution of 0.37 mmol of **3** in 3 mL of CCl_4 for 6 h until all the reactants were carried through a pyrolysis tube heated to 120–125 °C, depending on the experiment. The temperature was monitored with a thermocouple. The effluents were condensed in a −75 °C trap. Upon completion of the pyrolysis, 0.8 mL of DMAD was added to the trap, and the resulting solution was stirred at 20 °C for 16 h under N_2. The volatiles, which by NMR contained no dienes, were removed on a vacuum line at 0.5 torr. The residual mixture of adducts was separated by HPLC. Only **4** and **5** were present; neither **6** nor **7** was detected.

Preparation of 3a. A solution of the isodicyclopentadienyl anion **8** was prepared and quenched as previously described except for the substitution of DOAc for HOAc. The DOAc was prepared by reacting dry Ac_2O, freshly distilled from fused NaOAc, with 1 equiv of D_2O (99.8% D). The ratio of **3a** to **1**-d_1 was 1.6:1. Diene **3a** was purified as previously described. Mass spectral analysis of the DMAD adduct established that

(32) To date, the preferential endo product orientation resulting from electrophilic substitution at C_4 of the isodicyclopentadienyl anion (**8**) suggests that this σ/π interaction may also control the ionic reaction course of the isodicyclopentadienyl system. For example, we found that analysis of the ^{1}H NMR signals corresponding to the syn and anti hydrogens of the DMAD adduct of **1a**, generated by deuteration of anion **8** with HOAc-d_1 at 0 °C, revealed that endo attack was favored by 1.7:1. Likewise Bartlett found that a −75 °C quench of **8** with MeOD/THF favored protonation at C_4 from the endo face by 4.7:1.[19] Paquette reported a similar preference of ~5:1 for endo deuteration of **8** with D_2O/THF at −75 °C.[33] Also trapping **8** with MeI generated only **3** methylated at C_4 exclusively from the endo face; similar specificity was observed for spiroannulation of **8** with labeled 1,4-chloroiodobutane. Model reactions have yet to be run to delineate the importance of solvation, electrostatic interactions, and charge-induced dipole and steric interactions which could have contributed to the preferential endo attack.

(33) Paquette, L. A.; Charumilind, P.; Kravetz, T. M.; Bohm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1983**, *105*, 3126.

0.96 D had been incorporated. The ^1H NMR spectrum of **3a** differed from that reported for **3** only in that the singlet at δ 3.0 integrated for 1 H.

Gas-Phase Pyrolysis of 3a. The gas-phase pyrolysis of 0.2 mmol of **3a** in 2 mL of CCl_4 was run at 126 °C as described for **3**. Adduct **4a**, after purification by HPLC, contained 0.96 D by mass spectrometry. The ^1H NMR spectrum of **4a** was identical with that of **4** except that the signal at δ 3.6 integrated for 7 instead of 8 H and the two signals at δ 2.4 and 2.05 appeared as doublets of doublets instead of as doublets of triplets. The ^2H NMR of **4a** contained signals at δ 3.6 and 2.05 in a ratio of 15:1.

The pyrolysis of **3a** was repeated under identical conditions except that the pyrolysis tube was packed with Pyrex beads. Identical results were obtained.

Determination of the 1° Isotope Effects for the Conversion of 3 to 2. A known mixture of **3** and **3a** was pyrolyzed in the gas phase at 122 °C under previously described conditions. The effluent containing both **1** and **3** was trapped with DMAD. The deuterium contents of purified **4** and **6** were determined by mass spectrometry, and the isotope effect was calculated. The values obtained for four separate experiments were 1.92, 1.93, 2.0, and 1.82 (average 1.92 ± 0.07).

Preparation of 3b. D_2O (41 mL) was slowly added to a stirred suspension of 0.42 g (10.7 mmol) of potassium in 130 mL of HMPA at 0 °C under N_2. After H_2 evolution ceased, 83 mmol of **1** in 10 mL of benzene was added, and the solution was stirred for 22 h at 50 °C. The reaction mixture was cooled, quenched with 3 mL of DOAc, poured into H_2O, and extracted three times with hexane. The combined extracts were washed four times with H_2O and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the product was dissolved in 15 mL of benzene. For complete incorporation of four deuteriums into **1**, the above product was resubmitted to the above conditions. Reisolation of the product yielded (40%) tetradeuterated **1**, which by mass spectrometry contained ~4.0 D.

Diene **1**-d_4 was converted to a mixture of **3b** and **1**-d_3 by sequential treatment with *n*-BuLi and HOAc as previously outlined. The mixture was separated as before by selective cycloaddition of **1**-d_3 with DMAD. By mass spectrometry the deuterium content of **3b** was 3.0 D. The NMR spectrum of the trideuterated **4** formed was identical with that reported for **4** except that the two doublets of triplets centered at δ 2.4 and 2.05 collapsed to singlets integrating for 0.55 and 0.45 H and the singlet at δ 3.6 integrated for 6 rather than 8 H.

Gas-Phase Pyrolysis of 3b. The pyrolysis of **3b** was run at 121 °C as previously described. The adducts were trapped with DMAD and purified; mass spectrometry revealed that **4b** contained 3.0 D. Adduct **4b**: ^1H NMR (CCl_4) δ 3.6 (s, 6.75 H), 2.92 (s, 2 H), 2.05 (s, 0.25 H), 1.4-1.4 (m, 4 H), 0.5 (m, 2 H).

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Bis(histamino)cyclodextrin–Zn–Imidazole Complex as an Artificial Carbonic Anhydrase

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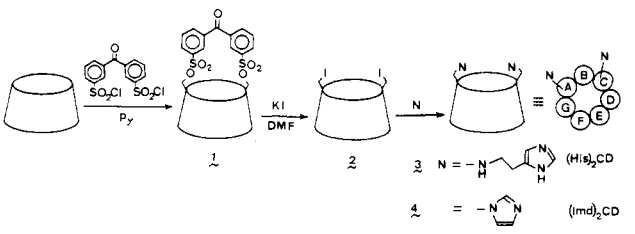
Contribution from Kyoto University, Department of Synthetic Chemistry, Yoshida, 606 Kyoto, Japan. *Received September 28, 1983*

Abstract: As a carbonic anhydrase model, bis(histamino)-β-cyclodextrin, $(His)_2CD$, was prepared from benzophenone-3,3′-disulfonate capped cyclodextrin. The association constant of Zn^{2+} with $(His)_2CD$ was determined to be $(4.5 \pm 2) \times 10^2$ M^{-1} at pH 7.5. The detailed kinetic analysis of the CO_2 hydration in imidazole buffer showed that $(His)_2CD \cdot Zn^{2+} \cdot Imd$-catalyzed CO_2 hydration where the observed catalytic constant was in the order of 10^3 M^{-1} s^{-1}. Free $(His)_2CD$, however, was rapidly converted to the corresponding carbamate, leading to a decrease in the catalyst concentration. Furthermore an unusual reaction of an indicator, *p*-nitrophenol, was observed only when $(His)_2CD \cdot Zn^{2+} \cdot Imd$ was present. Competitive bicarbonate inhibition and protonation of the catalyst are also important for understanding both the sharp rate decrease during the course of the hydration and the negligible catalysis of bicarbonate dehydration.

Carbonic anhydrase is an enzyme widely distributed in plants, bacteria, and mammals, catalyzing the interconversion of CO_2 and HCO_3^-. This enzyme is well recognized as one of the typical Zn^{2+}-containing enzymes. Zn^{2+} is known to be bound to three imidazoles arranged in a nonplanar orientation. Because of the physiological importance of CO_2 hydration and the large rate acceleration, much attention has been focused on the interesting nature of this enzyme.[1] Although the structure,[2] spectroscopy,[3] and kinetics[4] of the enzyme have been investigated in detail, the mechanism of the catalysis has not yet been satisfactorily clarified. In spite of the particular attention to native carbonic anhydrase itself, there is only a limitted number of studies available on artificial models actually catalyzing CO_2 hydration.[5] Recent

Scheme I



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