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Theoretical Evaluation of Epimerization in Diels–Alder Cycloadducts[1a]

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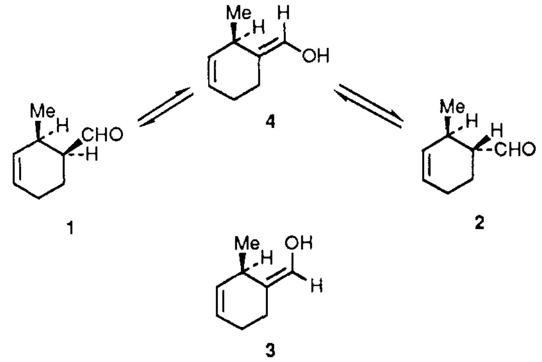
Four Diels–Alder reactions of *trans*-1,3-pentadiene (*trans*-piperylene) with acetone, methyl vinyl ketone, methyl acrylate, and acrylonitrile were selected for this study due to their varying epimerization rates previously reported (*J. Org. Chem.* **1988**, *53*, 5348). The reaction coordinate of the epimerization process for each reaction is evaluated for thermal and Lewis acid catalyzed conditions. The theoretical calculations are carried out by semiempirical (AM1) and ab initio (HF/STO-3G,3-21G) methods, and the computational results were found to be in agreement with the experimentally observed substituent effects on the relative rates for epimerizations. Due to the enhancement of epimerization by silica gel, the possibility of inadvertently altering the product distribution of a Diels–Alder reaction by GC and column chromatography is also discussed.

Introduction

The Diels–Alder reaction is considered to be one of the most important methods to generate six-membered rings in synthetic organic chemistry.[2] This reaction not only is one of the few that can generate C–C bonds directly but also is remarkably versatile due to the large numbers of building blocks (dienes and dienophiles) that can be utilized.[3] A characteristic of the Diels–Alder reaction that makes it particularly important for synthetic purposes is that up to four contiguous chiral centers can be developed simultaneously under relatively mild conditions.[4]

Diels–Alder reactions with 1-substituted butadienes and nonsymmetrical dienophiles can give up to four cycloadducts. These are the two regioisomers (which we will term ortho and meta for the 1,2- and 1,3-substituted cycloadducts, respectively) with each having two stereoisomers (endo and exo, i.e., **1** and **2**, respectively, in Scheme I). Under kinetic control, normal-electron-demand[5] Diels–Alder reactions of 1-substituted butadienes generally yield the ortho regioisomer with the endo stereoisomer being the major product even though the exo isomer is usually the thermodynamically favored one.[6]

Scheme I



Several explanations have been reported in the literature for the formation of the contrathermodynamic endo product. These are in chronological order (1) the Alder rule "maximum accumulation of unsaturation", which predicts the endo transition state to have a lower energy,[7a] (2) secondary orbital interactions stabilizing the endo transition state,[7b] (3) geometry constraints favoring the primary orbital overlap for the endo transition state,[7c] (4) attractive van der Waals dispersion forces favoring the endo product,[7d] (5) repulsive forces disfavoring the exo product,[7e] and (6) combination of steric effects and secondary orbital interactions influencing the stereoselectivity.[7f] Of course caution has to be exercised in determining the stereoselectivities, since the thermodynamically stable product may be unintentionally formed by epimerization of the cycloadducts during (or after) the reaction. Occasionally however, enolization without epimerization may occur for a stereoisomeric equilibrium if it is under thermodynamic control.[8] While the need for careful determination of the product distribution due to possibility of epimerization has been recognized as early as 1962,[9] no significant theoretical studies have been carried out to investigate this process.

The effect of Lewis acid catalysis on the Diels–Alder reaction has also been exhaustively investigated, both experimentally[10] and theoretically.[11] However, the fate

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of the reaction products, after the reaction is completed, has not been addressed as rigorously. In fact, while epimerization is known to be enhanced by acid catalysis,[12] no theoretical study was undertaken to understand the extent of epimerization for different cycloadducts under the influence of Lewis acid catalysis.

Experimentally, isomerization of an electrocyclic cycloadduct from the kinetically favored Z to the thermodynamically preferred E isomer has been observed.[13] Jaeger et al. showed that epimerization of amphiphilic diacids in aqueous base can be catalyzed by cationic micelle- and bilayer-forming surfactants.[14] Epimerization of cheletropic cycloadducts, from endo to exo products under moderate temperatures (60–80 °C), has also been demonstrated.[15] Epimerization of the Diels–Alder cycloadducts of thermal reactions, however, is usually not observed under mild conditions (i.e., room temperature).[16] More rigorous reaction conditions and/or the presence of a strong base or acid are needed to initiate conversion to the more stable exo isomer.[16a,c,d] For example, Overman and Jessup have reported epimerizations for some Diels–Alder cycloadducts at temperatures around 110 °C.[17]

Recently, we noted rapid epimerization for the reaction between *trans*-1,3-pentadiene and a series of dienophiles at room temperature in the presence of a Lewis acid.[18] The cycloadducts with acrolein attained complete equilibrium within 25 min, whereas with methyl vinyl ketone, they reached equilibrium in 5 days. The cycloadducts with methyl acrylate did not get to equilibrium even after 6 days, although substantial epimerization was observed. Finally, the cycloadducts with acrylonitrile did not show any epimerization at all, under similar reaction conditions. Consequently, the following sequence of dienophile substituent effect has been obtained with respect to their influence to the epimerization rates: $CHO > COCH_3 > COOCH_3 \gg CN$. Under noncatalyzed conditions, the cycloadducts obtained from the reaction of *trans*-piperylene and acrolein reached epimerization equlibrium within 30 days at room temperature.[18]

In this study, a theoretical evaluation of epimerization was carried out for the above series of Diels–Alder reactions, and the computational results are compared to the experimental findings.

Computational Methods

Molecular orbital calculations at the semiempirical level were carried out with the AMPAC program[19] utilizing the AM1 method.[20]

Table I. Ab Initio Energies (au) and Relative Energies (kcal/mol)

struct	HF/STO-3G	E_{rel}	barrier	HF/3-21G	E_{rel}	barrier
1	−380.05891	1.7		−382.62924	3.0	
2	−380.06161	0.0		−382.63400	0.0	
3	−380.03362	17.6	15.9	−382.61196	13.8	10.8
4	−380.03526	16.5	14.8	−382.61410	12.5	9.5
5	−418.64216	4.1		−421.45324	4.6	
6	−418.64866	0.0		−421.46062	0.0	
7	−418.61763	19.5	15.4	−421.43456	16.4	11.8
8	−418.61045	24.0	19.9	−421.42595	21.8	17.2
9	−492.50393	1.7		−495.91948	1.7	
10	−492.50661	0.0		−495.92215	0.0	
11	−492.46085	28.7	27.0	−495.87272	31.0	29.3
12	−492.45938	29.6	27.9	−495.86912	33.3	31.6
13	−359.38692	0.8		−361.76702	0.7	
14	−359.38820	0.0		−361.76819	0.0	
15	−359.30313	52.6	51.8	−361.70627	38.9	38.2

Ab initio geometry optimizations were conducted with the GAUSSIAN-86 program[21] using the HF/STO-3G minimal basis set,[22] followed by single-point calculations with the split-valence HF/3-21G[23] basis set. All geometries for the cycloadducts and intermediates were fully optimized without any symmetrical restrictions (i.e., C_1 point group). For each of the cycloadditions between *trans*-piperylene and acrolein, methyl vinyl ketone, and methyl acrylate, two enol intermediates were calculated for the ortho regioisomer: one having the OH group syn to the methyl ring substituent and the other carrying the OH group in the anti position. However, for the reaction with acrylonitrile only one intermediate was calculated since C═C═NH is linear and there is no syn/anti isomerization. Consequently, geometries of eight cycloadducts and seven intermediates were optimized for both noncatalyzed (AM1, STO-3G) and catalyzed (AM1) structures. The Lewis acid complexes were calculated by fully optimizing the geometries with a BH_3 group attached to the carbonyl oxygen.

Results and Discussion

Experimentally, the ortho regioisomers are determined to be the major products in all four reactions. Therefore, only the stereoisomers for ortho adducts are evaluated in this study. For practical purposes, the term "pseudopotential barrier" will be used in this text to describe the energy gap between the endo adduct and the low lying intermediate that connects the two cycloadducts. Although the transition structures[24] between the stereoisomers and intermediates have not been calculated due to excessive cpu demand, these structures are assumed to be similar to the intermediates both geometrically and energetically, in line with the Hammond's postulate.[25] It is not uncommon to use local minima to describe a reaction without actually carrying out the explicit calculations on the transition states, particularly when these calculations require very large amounts of cpu even with the use of supercomputers. For example, using only local minima, the zinc hydride complexation mechanism to formaldehyde was recently analyzed.[26] Hence, we believe that the

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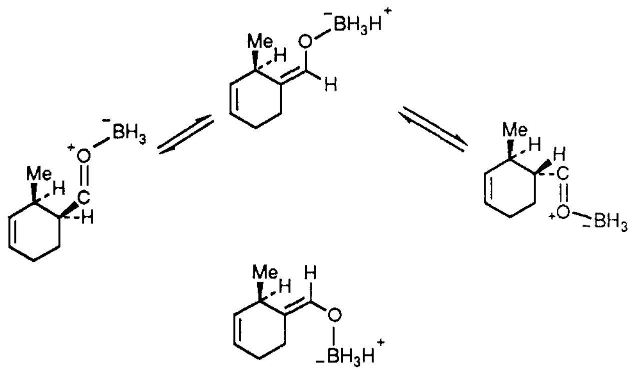
Scheme II

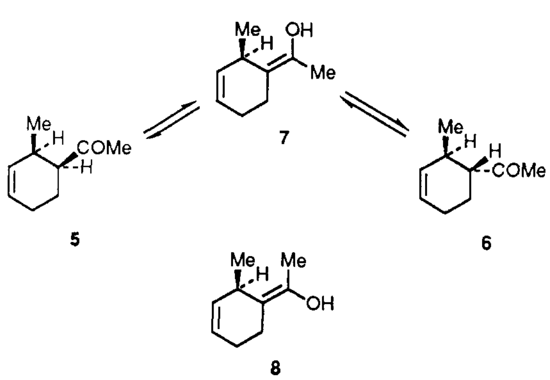


pseudopotential barriers give a reasonable impression of the actual potential barriers.

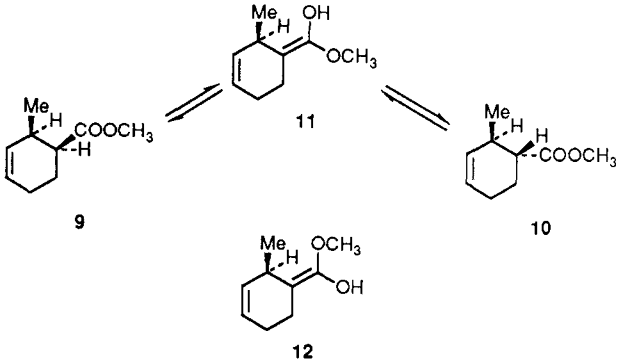
The geometry optimizations were carried out with the HF/STO-3G minimal basis set, which is known to be effective in predicting geometries for organic molecules[27] but inadaquate for determining accurate energetics.[28,29] In a recent study, Houk critically evaluated the structural properties and energetics for the electrocyclic ring opening of cyclobutene using different theoretical methods; he concluded that the optimized geometries obtained from all methods studied were in good agreement with the MP2/6-31G* optimized structures; however, energetics were much more dependent on the method of calculation.[29] The unrealistically high activation energies obtained with HF/STO-3G reduced significantly with the HF/3-21G basis set, which yielded activation barriers comparable to those obtained with higher levels of Hartree–Fock theory.[29] Therefore, to compensate for the limitations of HF/STO-3G energies, single-point calculations were carried out with the HF/3-21G split-valence basis set. The ab initio energies for the cycloadducts and the intermediates, relative energies, and pseudopotential barriers are listed in Table I.

For the investigation of organic reaction mechanisms, semiempirical calculations that involve approximations to the Hartree–Fock equations are also frequently used. Dewar's MINDO/3, MNDO, and AM1 methods usually give results in good agreement with experimental observations.[20] Of these methods, the latest version, AM1, in general is found to give activation energies closest to the experimental findings.[29,30] Therefore, in addition to the ab initio calculations, we also carried out full geometry optimizations for all cycloadducts and intermediates (with and without BH_3 complexation), using the AM1 method. This is particularly important for the Lewis acid complexes, which structures were beyond the scope of an ab initio investigation. These complexes were modeled by optimizing the structures with a BH_3 attached to the carbonyl oxygen as shown in Scheme II. The AM1 heats of formations and pseudopotential barriers are listed for thermal and catalyzed structures in Table II.

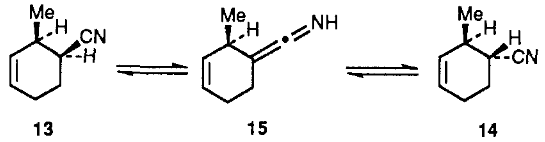
Scheme III



Scheme IV



Scheme V



Vibrational frequency calculations were performed at the semiempirical level on all structures. Since none of these structures possessed any negative force constant (on the diagonalized Hessian matrix), all structures **1–15** (with and without BH_3 complexation) are equilibrium structures (minima) on the AM1 potential energy surface. We recognize that a deficiency of the AM1 method to reflect substituent effects for similar reactions has been noted[29,31,32] and that such effects have also been shown to be well calculated with ab initio theory at the 3-21G level.[32] Therefore, we report results obtained from both ab initio (Table I) and semiempirical (Table II) calculations for completeness. As expected, the pseudopotential barriers are relatively large with HF/STO-3G, smaller with HF/3-21G, and still smaller with the AM1 method. With all three computational methods, however, the calculated trends in epimerization rates are consistent with the experimental observations. We will now elaborate the energetic aspects of the epimerization process and substituent effects using ab initio theory and discuss the effect of Lewis acid catalysis with AM1 data.

Energetics for Epimerization. In the reaction between *trans*-1,3-pentadiene (*trans*-piperylene) and acrolein (Scheme I), the exothermicity for the epimerization of the endo-Diels–Alder adduct **1** to the exo-adduct **2** is calculated to be 3.0 kcal/mol (HF/3-21G). Of the two possible intermediates for this process, **4** is 1.3 kcal/mol more stable than **3**. The substantial steric interaction between the OH

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Table II. AM1 Heats of Formation and Relative Energies (kcal/mol)

	noncatalyzed			BH$_3$ catalyzed			
struct	ΔH_f	E_{rel}	barrier	ΔH_f	E_{rel}	barrier	$E_{complex}$[a]
1	-41.54	1.32		-33.12	0.99		-17.84
2	-42.86	0.00		-34.11	0.00		-17.51
3	-33.92	8.94	7.62	-46.77	-12.66	-13.65	-39.11
4	-38.02	4.84	3.52	-46.72	-12.61	-13.60	-34.96
5	-45.62	3.35		-37.71	3.35		-18.35
6	-48.97	0.00		-41.06	0.00		-18.35
7	-39.18	9.79	6.44	-49.05	-7.99	-11.34	-36.13
8	-38.77	10.20	6.85	-51.85	-10.79	-14.14	-39.34
9	-92.74	3.38		-78.06	9.59		-11.58
10	-96.12	0.00		-87.65	0.00		-17.79
11	-77.93	18.19	14.81	-86.62	1.03	-8.56	-34.95
12	-76.58	19.54	16.16	-86.04	1.61	-7.98	-35.72
13	20.24	1.67		25.79	1.37		-20.71
14	18.57	0.00		24.42	0.00		-20.41
15	39.18	18.94	17.27	27.07	2.65	1.28	-38.37

[a] The complexation energies are calculated by using AM1 ΔH_f = 26.26 kcal/mol for BH$_3$.

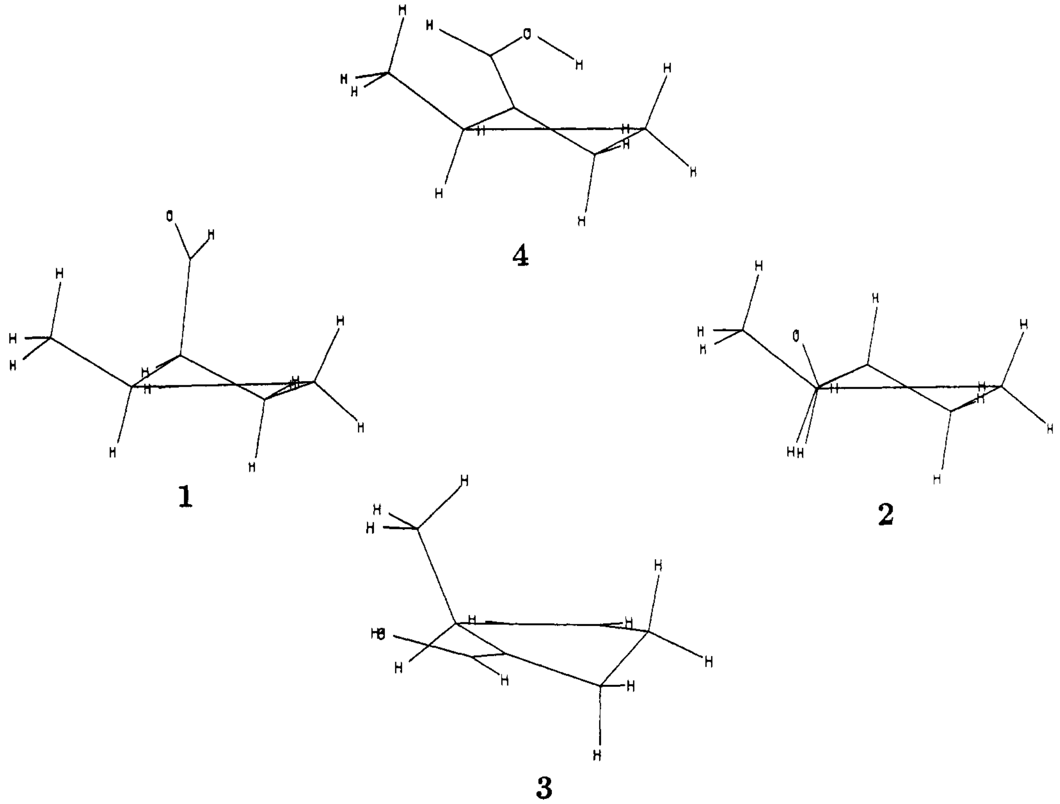

Figure 1. Optimized (HF/STO-3G) geometries of **1**–**4** displaying the half-chair conformations for **1**, **2**, and **4** and the boat conformation for **3**.

and CH$_3$ groups in **3** forces the cyclohexene ring to adopt a boat conformation. Structures **1**, **2**, and **4** favor the more stable half-chair conformation (Figure 1). The pseudopotential barrier for the epimerization through the lower lying intermediate **4** is 9.5 kcal/mol.

For the Diels–Alder cycloadducts (*endo*-**5** and *exo*-**6**) that result from the reaction between *trans*-piperylene and methyl vinyl ketone (Scheme III), the isomerization **5** → **6** is exothermic by 4.6 kcal/mol with a pseudopotential barrier (**7**) of 11.8 kcal/mol; the barrier for isomerization via **8** amounts to 17.2 kcal/mol.

Reaction between *trans*-piperylene and methyl acrylate yields adducts **9** (endo) and **10** (exo; Scheme IV). The exothermicity for the conversion **9** → **10** amounts to 1.7 kcal/mol with a pseudopotential barrier via **11** of 29.3 kcal/mol and a less favored pathway (31.6 kcal/mol) involving **12**. Finally, for the Diels–Alder reaction between *trans*-piperylene and acrylonitrile that results in the two adducts **13** (endo) and **14** (exo; Scheme V), the intermediate **15** is calculated to be 38.2 kcal/mol higher in energy than **13**, which is the thermodynamically favored product, allbeit by a mere 0.7 kcal/mol.

From the experimental data,[18] the extrapolated reactivity order for the Lewis acid catalyzed epimerization for substituents on the cycloadducts is obtained: CHO > COCH$_3$ > COOCH$_3$ ≫ CN. Even though some of the noncatalyzed epimerizations did not reach equilibrium (for durations in excess of a month), the same reactivity order for epimerization may be assumed. Our ab initio calculations give the same sequence as the experimental data; the calculated pseudopotential barriers for epimerizations are 9.5, 11.8, 29.3, and 38.2 kcal/mol for the CHO-, COCH$_3$-, COOCH$_3$-, and CN-substituted cycloadducts, respectively.

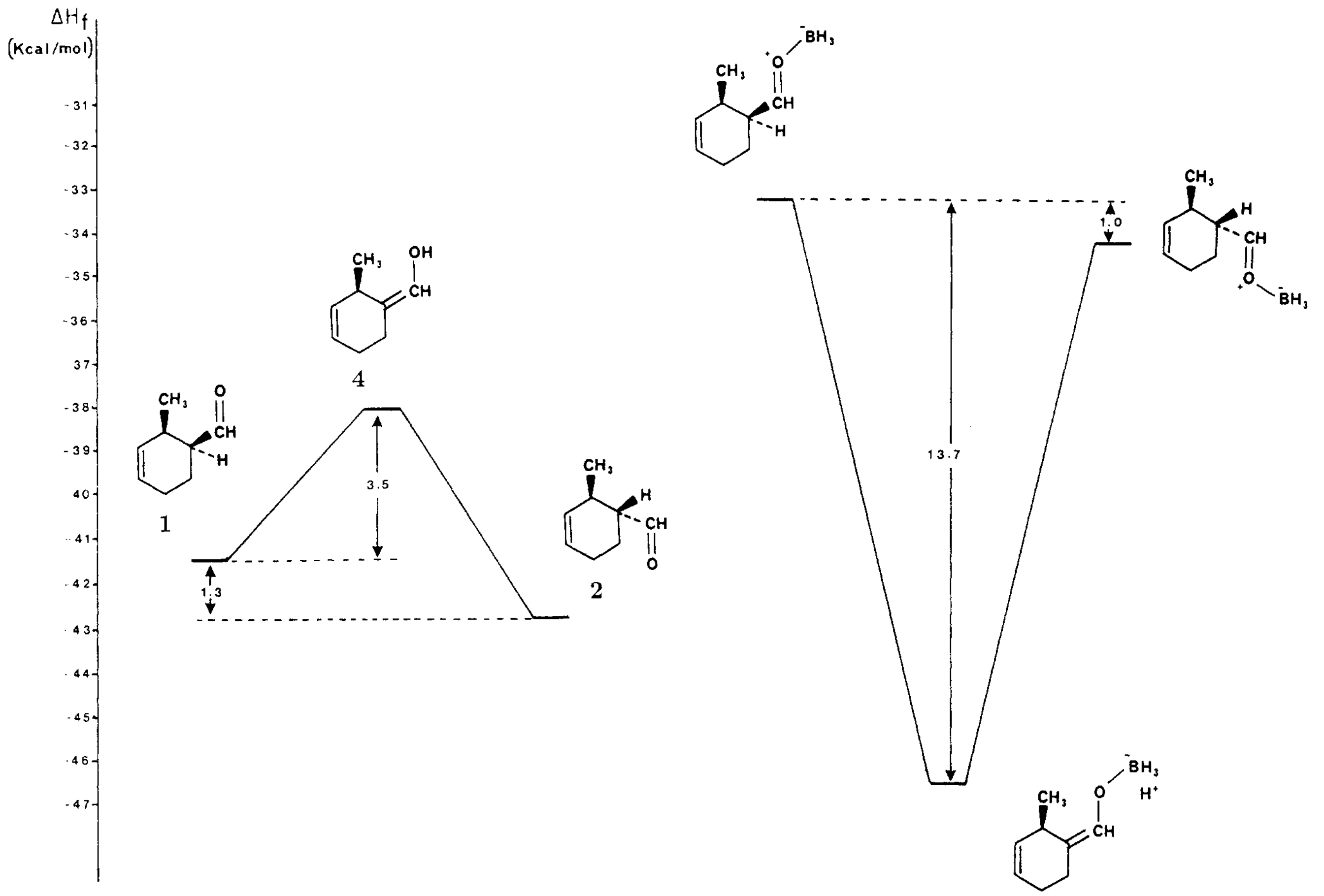

Figure 2. Schematic illustration of noncatalyzed versus catalyzed pseudopotential barriers (AM1) for the epimerization of 1 to 2.

Substituent Effects. To analyze the reactivity order for these epimerizations, it is instructive to evaluate the substituent effects, which traditionally are considered to be influenced by electronegativity, field, polarizability, and resonance effects.[33] Electronegativity effects can be viewed as the partial ionic character of a σ-bond between the substituent and its bonded atom of the molecular framework. Field effects are the combination of charge and dipole interactions between the substituent and the polarized bonds of the framework. Polarizability effects are charge- or dipole-induced interactions between the substituent and the molecular framework. Finally, resonance effects involve π-electron bonding and delocalization between the substituents and molecular framework.[33] The substituent parameters (σ) for CHO, $COCH_3$, $COOCH_3$, and CN are −0.05, −0.04, 0.04, and 0.30 (electronegativity), 0.31, 0.26, 0.24, and 0.60 (field), −0.46, −0.55, −0.49, and −0.46 (polarizability), and 0.19, 0.17, 0.16, and 0.10 (resonance effects), respectively.[33] The field and resonance effects do follow the experimentally observed trend for the carbonyl-substituted cycloadducts. All of the other effects are comparable for the carbonyl substituents but single out the nitrile group. This may be expected since nitrile → ketenimine reactions have higher barriers than the corresponding enolizations.

Since epimerizations proceed via a two-step enolization, the acidities of the enolizable protons must play an important role in the stabilities of the keto forms. The pK_a values for acetaldehyde,[34] acetone,[35] and ethyl acetate[36] are 17, 19, and 25, respectively; it follows that the more labile the carbonyl proton is, the faster the epimerization, which is in harmony with the experimental observations. The carbonyl double bond is also stabilized by π-donating and σ-accepting substituents,[37] and hence the epimerization process is slowed down the most with the $COOCH_3$ group and less with $COCH_3$, as compared to the CHO-substituted cycloadducts. This trend is in line with the ability of these substituents to activate olefins. Recently, Roush reported the same trend with carbonyl substituents for increasing stereoselectivity of the intramolecular Diels–Alder reaction of terminally activated trienes; this selectivity was enhanced even more by Lewis acid catalysis.[38]

Effect of Lewis Acid Catalysis. The important difference between the uncatalyzed and the Lewis acid promoted epimerization lies in the stabilization of the enolized intermediates. The BH_3 complexed intermediates are energetically favored over the endo cycloadducts by 13.6 (CHO), 11.3 ($COCH_3$), and 8.6 ($COOCH_3$) kcal/mol, except for the CN derivative, which still has a small pseudopotential barrier of 1.3 kcal/mol. These intermediates are also more stable than the thermodynamic CHO- and $COCH_3$-substituted exo cycloadducts by 12.7 and 8.0 kcal/mol, respectively, but not for $COOCH_3$ and CN derivatives, although these energy differences amount to only 1.0 and 2.7 kcal/mol, respectively. Clearly, Lewis acid

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complexation has a dramatic impact on the kinetics of the epimerization, as the pseudopotential barriers either reduce substantially (e.g., CN) or even vanish, and instead results in a potential sink for the enol intermediate (e.g., CHO and $COCH_3$; see Figure 2). Interestingly, the BH_3 complexation of all cycloadducts are similar and amount to a stabilization of 17–20 kcal/mol (average 17.8 kcal/mol). However, while the stabilizations of all enol intermediates are also similar to each other, the magnitude of stabilization is twice that of the keto cycloadducts, i.e., 35–39 kcal/mol (average 36.9 kcal/mol). It is relevant to note that the exothermicities for epimerizations are hardly effected by BH_3 complexation; the corresponding energy differences are 1.3 → 1.0 kcal/mol for CHO, 3.4 → 3.4 kcal/mol for $COCH_3$, 3.4 → 9.6 kcal/mol for $COOCH_3$, and 1.7 → 1.4 kcal/mol for CN substituted cycloadducts. Consequently, the major influence of Lewis acid catalysis in epimerizations can be generalized as a substantial relative stabilization (16–20 kcal/mol) of the enol intermediates, thereby increasing the epimerization rate.

Acceleration of Diels–Alder reactions on the surface of silica gel and aluminum oxide has been known for some time.[39] In fact, Veselovsky et al. have reported a dramatic acceleration of the Diels–Alder reaction by adsorption on chromatographic adsorbents.[40] Recently, isomerization of (*Z*)-vinylsilanes into the *E* isomer has been described by using silica gel as an additive.[41] Experimentally, we have observed epimerization of some of the Diels–Alder cycloadducts when they were subjected to gas and column chromatography.[18b] Our theoretical calculations indicate that the effect of Lewis acids such as chromatographic adsorbents are limited not only to the cycloaddition reactions but also to the distribution of the reaction products during analysis. Since some of the cycloadducts epimerize rapidly at room temperature, inadvertent alteration of the product distribution of a Diels–Alder reaction by GC and column chromatography, which are routinely used for separation and identification purposes, is possible.

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Registry No. **1**, 873-30-3; **2**, 766-48-3; **3**, 123883-56-7; **4**, 123883-57-8; **5**, 55169-92-1; **6**, 55169-93-2; **7**, 123883-58-9; **8**, 123883-59-0; **9**, 22973-22-4; **10**, 7605-51-8; **11**, 123883-60-3; **12**, 123883-61-4; **13**, 57278-90-7; **14**, 57278-89-4; **15**, 123883-62-5; BH_3, 13283-31-3.

Supplementary Material Available: GAUSSIAN-86 archive entries for the cycloadducts and intermediates (**1**–**15**) fully optimized with HF/STO-3G basis set (6 pages). Ordering information is given on any current masthead page.

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Conformational Analysis of 5-Substituted 1,3-Dioxanes. 2. Phenylthio and Cyclohexylthio Groups and Their Sulfinyl and Sulfonyl Derivatives[1]

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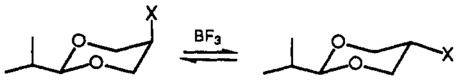
The positions of equilibrium, established by acid catalysis, between diastereomeric *cis*- and *trans*-5-(phenylthio)- (**7**), 5-(phenylsulfinyl)- (**8**), 5-(phenylsulfonyl)- (**9**), 5-(cyclohexylthio)- (**10**), 5-(cyclohexylsulfinyl)- (**11**), and 5-(cyclohexylsulfonyl)-2-*tert*-butyl-1,3-dioxanes (**12**) are reported and compared with published data for the 5-(methylthio)- (**1**), 5-(methylsulfinyl)- (**2**), 5-(methylsulfonyl)- (**3**), 5-(*tert*-butylthio)- (**4**), 5-(*tert*-butylsulfinyl)- (**5**), and 5-(*tert*-butylsulfonyl)-2-isopropyl-1,3-dioxanes (**6**). Although ΔG° values for sulfides **1**, **4**, and **7** are very similar, there exist significant differences in the conformational behavior of the sulfoxides and the sulfones, which result from the relative steric, electrostatic, and torsional effects arising from each substituent. The information at hand (^{1}H and ^{13}C NMR spectroscopic data, X-ray crystallographic analysis, etc.) shows that, while sulfone *cis*-**6** has the *S*-*tert*-butyl group outside the ring, with both sulfonyl oxygens above the dioxane ring and eclipsing the endocyclic C–C bonds, the alkyl and aryl substituents in *cis*-**3**, *cis*-**9**, and *cis*-**12** point inside the ring. The phenylsulfonyl-inside rotamer in *cis*-**9** leads to steric and electron/electron repulsion that overcomes the electrostatic attractive interactions between the (negative) endocyclic oxygens and the (positive) sulfur in the sulfonyl group, so that equatorial *trans*-**9** predominates at equilibrium, $\Delta G^\circ = -0.44$ kcal/mol. All sulfoxides place both the sulfinyl oxygen and the substituent outside the dioxane ring.

Introduction

Several years ago, Eliel and co-workers[3] described the conformational equilibria of a large number of 2-isopropyl-5-X-1,3-dioxanes (eq 1).



(1)

Of particular interest was the conformational behavior of the sulfur-containing substituents: while the methylthio group shows a large preference for the equatorial orientation, the methylsulfinyl and the methylsulfonyl derivatives are predominantly axial at equilibrium.

Substitution of a *tert*-butylthio for the methylthio group had no significant effect on the ΔG° value,[1] whereas the

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