Asymmetric Diels-Alder Reactions with Chiral Dienes. Control of Facial Selectivity through Hydrogen Bonding

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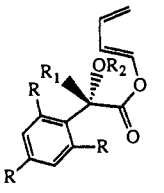
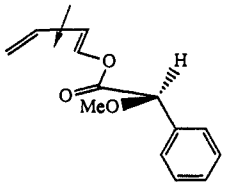
In recent years, attempts have been made to achieve ground-state binding of two reacting species with a nonenzyme receptor to mimic enzyme catalysis.[1-3] Herein we report the power of *intermolecular hydrogen bonding* in asymmetric Diels-Alder reactions of a diene, serving as a receptor to an array of dienophiles, which confers the ability to exhibit high asymmetric induction at room temperature without employing any Lewis acid catalyst.

Our interest in studying and identifying the chiral control elements in the quite remarkably diastereoselective Diels-Alder reactions of Trost's diene (**1a**)[4,5] led us to propose a model in which





1a $R_1 = H$, $R_2 = Me$, $R = H$
1b $R_1 = Me$, $R_2 = H$, $R = Me$
1c $R_1 = Me$, $R_2 = TMS$, $R = Me$

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the diene adopts a nearly perpendicular conformation (**2**) in the transition structure.[6] The essential features of this perpendicular model are that the dienyl and ester carbonyl groups are coplanar, the C-O bond remains proximal to the carbonyl, and the phenyl group adopts a nearly perpendicular orientation. Stereodifferentiation is caused by preferential approach of the dienophile to the less hindered face of the diene, opposite to the phenyl ring. In a program to provide further mechanistic insight as well as to achieve high asymmetric induction at room temperature, we undertook the task of designing the stereogenic center of the mandelate chiral auxiliary. After considerable experimentation, we found a suitable diene for our purpose, **1b**, which has additional methyl substitutions on the chiral auxiliary. We synthesized racemic diene **1b** and its protected analogue **1c** by a route similar to the methods of Trost[4,5] and Paquette.[7]

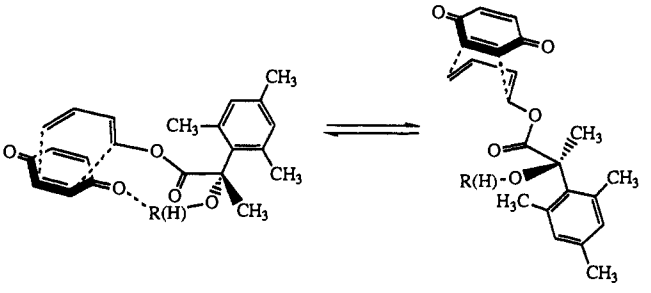
The design concept of this diene was based on the hypothesis that the increase in the relative ground-state population of the perpendicular rotamer (**2**) would enhance both the shielding of the hindered face of the diene and the diastereofacial discrimination. Methyl groups at the ortho positions appear from molecular models to almost freeze the phenyl group of the mandelate into the perpendicular conformation. The α-methyl group should further rigidify the perpendicular model, and the hydroxy group might chelate to the carbonyl group of the dienyl ester function.

We have achieved remarkably high asymmetric induction in Diels-Alder reactions of diene **1b** at 25 °C *without employing any Lewis acid catalyst* (Table I). Most reactions showed a dramatic solvent effect (entries 3, 7, and 10) when the polar solvent DMF was employed. Reactions of the protected diene **1c** (entries 4 and 8) were extremely slow, but some reaction occurred with *N*-ethylmaleimide (entry 4). The *sense of facial selectivity changes upon protecting the hydroxy group of the chiral auxiliary* (entries 1 and 4)! TCNE does not show good selectivity (entry 11).

Table I. Diastereoselectivity in the Diels-Alder Reactions of **1b** and **1c** with Different Dienophiles at ca. 25 °C

entry	diene	dienophile	solvent	selectivity[a,11]
1	**1b**	*N*-ethylmaleimide	toluene	19:1[b]
2	**1b**	*N*-ethylmaleimide	toluene[c]	13.3:1[b]
3	**1b**	*N*-ethylmaleimide	DMF	3.3:1[b]
4	**1c**	*N*-ethylmaleimide	toluene	1:1.2[d]
5	**1b**	maleic anhydride	toluene	>15:1[e]
6	**1b**	benzoquinone	toluene	15.7:1[b]
7	**1b**	benzoquinone	DMF	3.8:1[b]
8	**1c**	benzoquinone	toluene	no reaction[f]
9	**1b**	naphthoquinone	toluene	9:1[b]
10	**1b**	naphthoquinone	DMF	4.3:1[b]
11	**1b**	tetracyanoethylene	toluene	4:1[b]
12	**1b**	tetracyanoethylene	DMF	no reaction[f]

[a] *Re:Si* on diene (cf. **3a**/**3b**). No exo adducts were observed. [b] By HPLC. [c] Molecular sieves (4 Å) added. [d] By hydrolysis of TMS group and then HPLC. [e] Estimated from 250-MHz ^{1}H NMR spectrum. [f] After 4 days, by 250-MHz ^{1}H NMR.



3a 3b

Figure 1. The two endo transition structures for the diene **1b** or **1c** with benzoquinone.

The most reasonable explanation of these results implicates two factors. We postulate (1) that the preferred diene conformation is disturbed by steric congestion from the additional methyl group at the stereogenic center as well as the *o*-methyl groups on the phenyl ring, forcing the diene to adopt another conformation (as in **3a**, Figure 1) in the transition structure. Houk et al. have shown that, for the diene **1a**, the rotamer with methoxy anti to the ester C=O is ~0.8 kcal mol^{-1} less stable than the syn one[8] (analogous to diene conformations as in **3a** and **3b**, respectively) in the ground state. For a protected diene such as **1c**, probably both rotamers are significantly populated (Figure 1); thus, the diastereoselectivity decreases (Table I, entries 4 and 8).

We also postulate (2) that the origin of the high selectivity observed in **1b** lies in transition-structure hydrogen bonding between the diene OH group and the *dienophile* C=O group. Solvent effects provide evidence: in DMF, H bonding is interrupted by solvation, decreasing facial selectivity. Analogous solvent effects were observed and interpreted in terms of H bonding in other Diels-Alder reactions of dienes bearing an allylic heteroatom.[9] Such H bonding would also favor a diene conformation as in **3a** (Figure 1), to permit coordination with the dienophile C=O group. It is reasonable that the preferred ester conformation in the Diels-Alder adduct should resemble that of the diene in the transition structure.[6] *The X-ray structure of the adduct (Figure 2) has an OH···O=C(dienophile) H···O distance of 1.839 Å (O-H···O angle 159.6°), which implies H bonding, the α-CH_3 eclipsing the ester C=O, and the phenyl anti to the dienophile moiety.*

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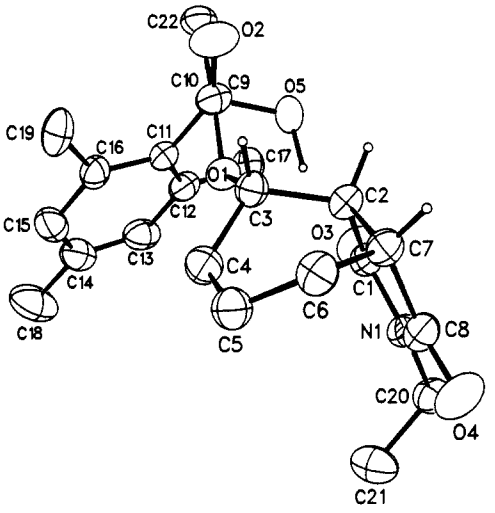

Figure 2. ORTEP diagram of the major cycloadduct (**4**) of diene **1b** with *N*-ethylmaleimide in toluene.

The elegant asymmetric Diels–Alder reactions of Masamune et al. provide a classic example of the use of *intramolecular* hydrogen bonding.[10] The present work shows that *intermolecular* hydrogen bonding with the dienophile carbonyl is preferred over intramolecular (with the ester carbonyl), and that equally high, and synthetically very useful, selectivity can also be obtained.[11]

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Supplementary Material Available: Tables of X-ray data, refined atomic positional and thermal parameters, bond distances, and bond angles (8 pages). Ordering information is given on any current masthead page.

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Layered Arrangement of Oriented Myoglobins in Cast Films of a Phosphate Bilayer Membrane[1]

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We describe herein a novel method for the layered arrangement of protein molecules by using synthetic bilayer membranes. Artificial organization of protein molecules should lead to many interesting possibilities. It is a key technology for developing protein-based electronic devices, and it can provide pseudonatural multienzyme systems as a new methodology in biotechnology.

Some years ago, Fromherz reported adsorption of cytochrome *c* to an arachidic acid monolayer and discussed its orientation based on polarized absorption spectra.[2,3] Two-dimensional crystallization of proteins on a monolayer was recently developed by Uzgiris and Kornberg.[4] Ringsdorf and co-workers used their approach to prepare 2D crystals of a streptavidin–biotin lipid monolayer.[5]

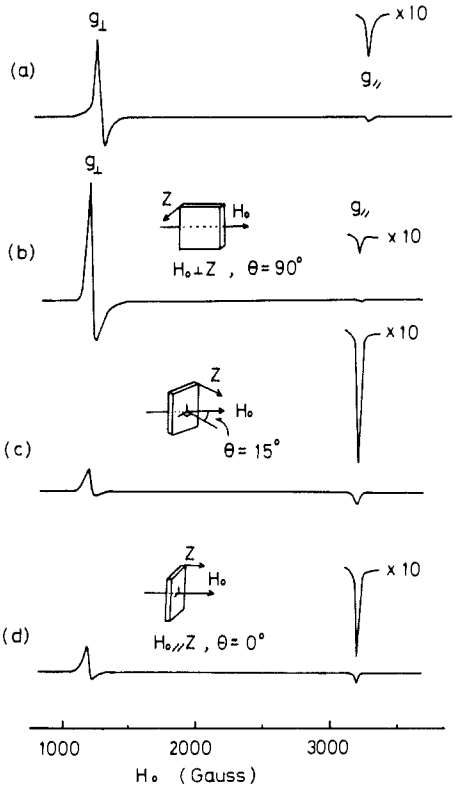
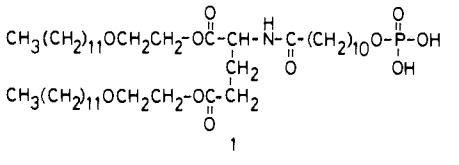


Figure 1. ESR spectra: (a) met-Mb powder; (b–d) met-Mb immobilized in a cast film of **1** ([met-Mb]/[**1**] = 1/160, pH = 7.5, 10 mM Tris·HCl). Spectral conditions: microwave power 5 mW, microwave frequency 9044 MHz, modulation frequency 100 kHz, modulation amplitude 7.9 G, time constant 0.03 s, scan time 4 min, temperature 4 K.

Matsumoto and co-workers prepared 2D crystalline monolayers of ferritin and F_1-ATPase on a clean mercury surface by self-association of the protein molecule.[6] Some membrane proteins were anisotropically immobilized in multilayer films of biolipids.[7] It is desirable to establish a more general methodology to be used for organizing protein molecules (water soluble as well as membrane bound) in controlled orientations.

As a first step toward this goal, we conducted immobilization of myoglobin in cast films of synthetic bilayer membranes. The heme group in myoglobin is a convenient probe for absorption spectral detection of denaturation and ESR spectral detection of protein orientation. Cast films of certain synthetic bilayer membranes were shown to possess highly regular multibilayer structures in which molecular orientation (microscopic anisotropy) is converted to macroscopic anisotropy.[8-12]

Synthetic amphiphile **1** was dispersed in 10 mM Tris·HCl buffer by sonication (pH = 7.5, 20 mM). Metmyoglobin (met-Mb, from horse heart) was then dissolved by gently shaking at room tem-



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