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DIELS-ALDER REACTIONS: RATE ACCELERATION PROMOTED BY A BIPHENYLENEDIOL

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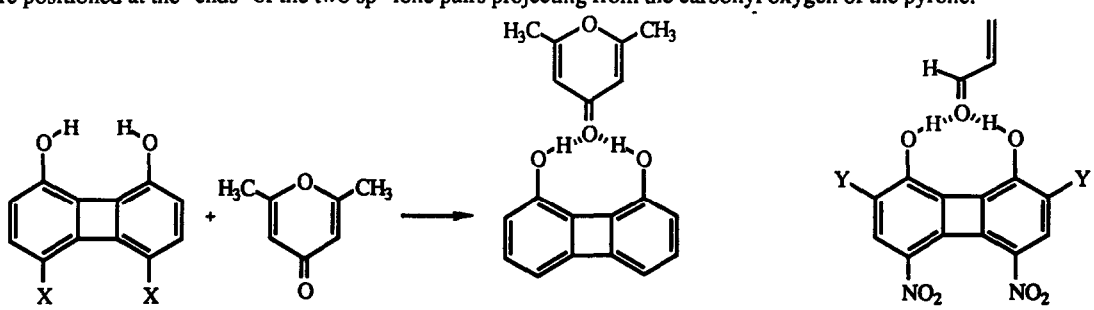
Abstract: *The presence of biphenylenediol 8 accelerates the rate of some Diels-Alder reactions. Catalysis via a complex involving two hydrogen bonds (see 6) is proposed.*

The development of catalysts for the asymmetric induction of Diels-Alder reactions is a subject of considerable current interest. To date, attention has focused almost exclusively on devising substances which function as chiral Lewis acids, but no general solutions have yet emerged.[1]

A putative alternate strategy for promoting asymmetric Diels-Alder reactions involves the use of hydrogen bonding to position (and activate) the dienophile within a chiral environment. The ability of hydrogen-bond-donating solvents to accelerate the rate of Diels-Alder reactions was recognized several decades ago,[2] but the possibility of using hydrogen bonding to control the outcome of Diels-Alder reactions has gone largely unexamined.[3,4,5]

In 1984, Hine and colleagues[6] reported that biphenylenediol **1** forms doubly hydrogen-bonded complexes with oxygen-bearing partners such as pyrone **2** (→**3**). In 1987, the more acidic dinitrobiphenylenediol **4** was shown to exceed **1** as a hydrogen bond donor.[7,8] X-Ray crystallographic studies[6a] have established that the pyrone ring in complex **3** is essentially coplanar[9,10] with the biphenylenediol ring system, and that the two hydrogen bonding protons of **1** are positioned at the "ends" of the two sp^2 lone pairs projecting from the carbonyl oxygen of the pyrone.



1, X= H
4, X= NO_2

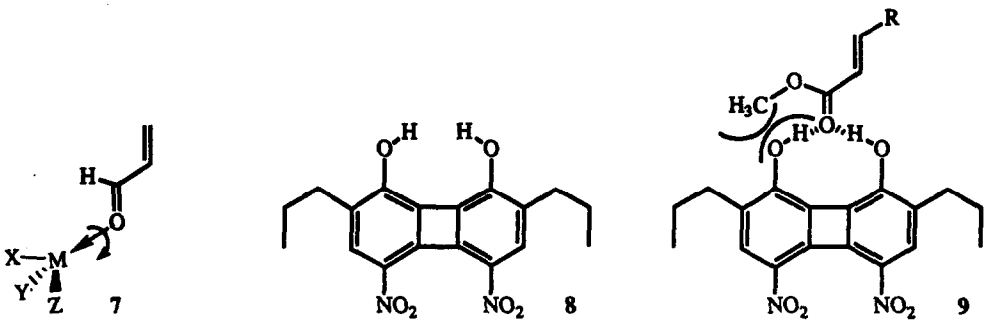
2

3

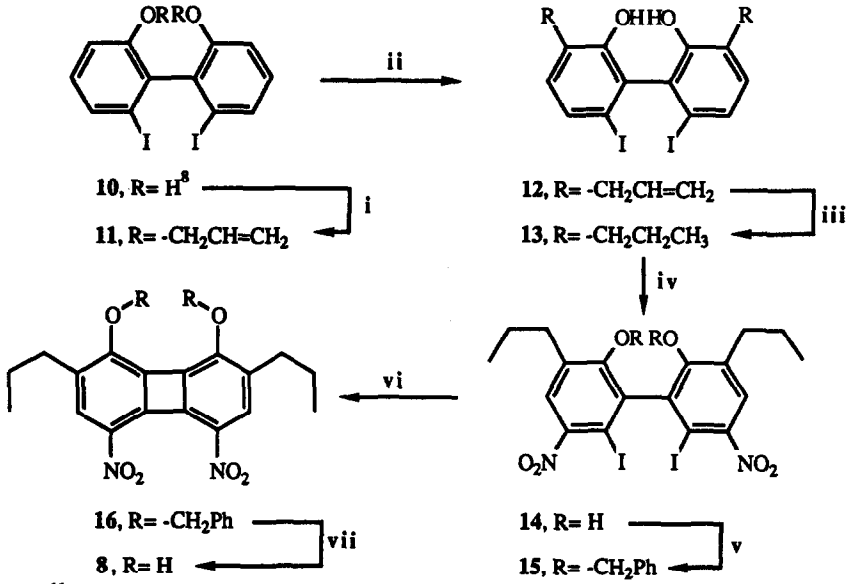
5, Y= H
6, Y= -$CH_2CH_2CH_3$

Extension of the concept underlying **3** suggested that if **1** - or better, **4** - were to temporarily bind (and thereby transiently activate) Diels-Alder dienophiles such as α,β-unsaturated aldehydes and ketones in a manner (see **5**) comparable to **3**, then incorporation of a **4**-like unit into an asymmetric environment might provide an effective chiral catalyst for Diels-Alder reactions. The bidentate nature of the binding of **1**/**4** is particularly attractive from a design standpoint, since it should impose on the complex (e.g., **5**) a relatively rigid geometry, thereby avoiding the conformational ambiguities which attend monodentate catalysts, represented in the generic, chiral Lewis acid case by **7**.

Before investing effort in the synthesis of a chiral version of **4**, prudence dictated an evaluation of the ability of the basic unit of **4** to accelerate the rate of Diels-Alder reactions. Diol **4** itself proved insufficiently soluble in inert solvents such as CH_2Cl_2 to be useful, but its dipropyl analog **8**, prepared (Scheme) by adaptation of the Hine-Ahn synthesis[8] of **4**, exhibited adequate solubility.



The effectiveness of **8** as a catalyst was assessed (^{1}H NMR, CD_2Cl_2 as solvent[12]) by simultaneously conducting pairs of experiments under conditions which were identical except that one of the two reaction solutions contained some **8**. An estimate of the effectiveness of **8** as a catalyst is provided by comparing the extent of product formation in the presence and absence of **8**. The results are summarized in the Table. Examination of the Table indicates that **8** promotes

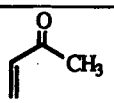
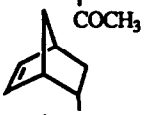
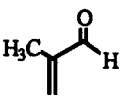
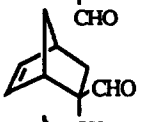
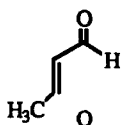
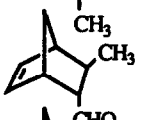
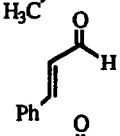
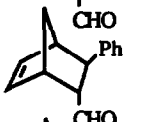
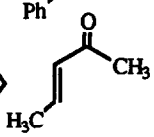
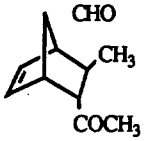
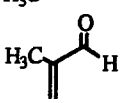
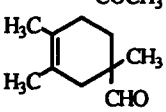
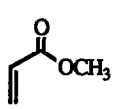
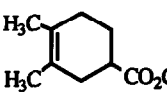
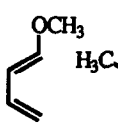
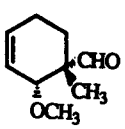
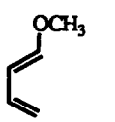
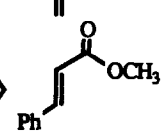


SCHEME:[11] Reagents: (i) CH_2=CH_2CH_2Br, K_2CO_3, acetone, Δ, 2 h; (ii) Double Claisen rearrangement: *N, N*-dimethylaniline, 200°C, 23 h; (iii) H_2 (~ 1 atm.), PtO_2, EtOH, 5 min; (iv) NO_2BF_4, AcOH, 2.5 h; (v) $PhCH_2Br$, K_2CO_3, DME-DMF (1:0.3); (vi) Cu-bronze, DMF, Δ, 4 h; (vii) BBr_3, C_6H_6, 3.5 h.

Diels-Alder reactions involving aldehydic and ketonic dienophiles (entries 1-7, 10) and exhibits turnover (several entries). In the case of ester dienophiles (entries 8, 11), significant rate acceleration is not observed, perhaps because the preferred *s*-trans conformations of esters inhibit complex formation as a consequence of repulsive interactions (see **9**). Not surprisingly, at least in one instance (entry 9) the presence in the diene of hydrogen-bond-accepting sites that are capable of competing for **8** with the dienophile, diminishes the effect of **8**.[18] Control experiments[20] using *p*-nitrophenol (pK_a 7.2[21]) and the more[20] acidic (pK_a 6.1[7]) 4-nitro-3-(trifluoromethyl)phenol in place of **8** (pK_a ~ 6.1[7,21]) indicated that both of the monoprotic controls are decidedly inferior to **8** as catalysts.[19,20]

The results in the Table, both positive and negative, are consistent with the intervention of hydrogen-bonded complexes such as **6**, and with the ability of such complexes to accelerate the rate of the Diels-Alder reaction. While those results do not *require* involvement of **6**-type complexes, they certainly encourage further study of the potential utility of hydrogen bonding in controlling the outcome of Diels-Alder reactions.

Table. Catalysis of Diels-Alder Reactions by 8[12]

Entry	Diene[a]	Dienophile	Temp/°C	Time	% product formation in absence of 8	% product formation in presence of 8 (mol. equiv. 8[b])	Product(s)[c]	Lit.
1			ambient	10 min	3	90 (0.4)		13
2			ambient	30 min	10	76 (0.4)		13
3			55	2 h	16	97 (0.5)		14
4			55	45 h[d]	21	95 (0.5)[e]		14
5			55	73 h[d]	13	74 (0.5)[e]		14
6			55	3 h	25	83 (0.4)		13
7			55	48 h	5	60 (0.5)[e]		14
8			55	120 h	7	10 (0.5)[e]		14
9			55	41 h	14[f]	26[f] (0.5)[e]		15
10			55	6 h	17[f]	77[f] (0.5)	Mixture of isomers	16
11			55	144 h[d]	13	13 (0.5)[e]	Mixture of isomers	17

(a) In excess[12]. (b) With respect to dienophile. (c) Major isomer given. (d) Additional diene was added at ~24 h intervals, because of competing diene dimerization. (e) Some catalyst decomposition was observed. (f) Some extra aldehyde proton resonance signals were observed in the NMR spectra which could not be attributed to either the Diels-Alder product or the dienophile.

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11. Mp and ^{1}H NMR ($CDCl_3$) data for new compounds. **11**: 87-88°C, δ 4.42-4.56 (m, 4H), 5.05-5.20 (m, 4H), 5.78-5.96 (m, 2H), 6.92 (dd, *J*=1.6 & 8.0 Hz, 2H), 7.05 (t, *J*=8.0 Hz, 2H), 7.54 (dd, *J*=1.6 & 8.0 Hz, 2H); **12**: 103-104°C, δ 3.44 (bd, *J*=4.8 Hz, 4H), 4.86 (s, 2H), 5.08-5.25 (m, 4H), 5.90-6.16 (m, 2H), 7.00 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=8.0 Hz, 2H); **13**: δ 0.98 (t, *J*=6.0 Hz, 6H), 1.58-1.78 (m, 4H), 2.50-2.72 (m, 4H), 4.73 (s, 2H), 7.00 (d, *J*=8.0 Hz, 2H), 7.50 (d, *J*=8.0 Hz, 2H); **14**: δ 1.00 (t, *J*=6.0 Hz, 6H), 1.50-1.90 (m, 4H), 2.50-2.85 (m, 4H), 5.45 (bs, 2H), 7.90 (s, 2H); **15**: 104-105°C, δ 0.86 (t, *J*=6.0 Hz, 6H), 1.45-1.64 (m, 4H), 2.44-2.68 (m, 4H), 4.65 (d, *J*=12.0 Hz, 2H), 4.80 (d, *J*=12.0 Hz, 2H), 6.88-6.97 (m, 4H), 7.15-7.24 (m, 6H), 7.65 (s, 2H); **16**: 108-109°C, δ 0.88 (t, *J* =6.4 Hz, 6H), 1.40-1.65 (m, 4H), 2.65 (t, *J*=6.4 Hz, 4H), 5.08 (s, 4H), 7.08 (s, 2H), 7.10-7.35 (m, 10H); **8**: 215-216°C (decomp.), δ 1.00 (t, *J*=6.4 Hz, 6H), 1.45-1.70 (m, 4H), 2.50 (t, *J*=7.2 Hz, 4H), 7.10 (s, 2H).
12. To a 0.011 or 0.014 M CD_2Cl_2 solution of **8** in an NMR tube the implicit (Table) quantity of dienophile and excess (10 equiv.) diene were added; the tube was sealed and maintained at ambient or 55°C. ^{1}H NMR (300 MHz) spectra were recorded at regular intervals and integrations of proper signals (identified using authentic[13-17] samples) were taken to measure the extent of product formation. Catalyst **8** was recovered in most of the cases by preparative tlc separation.
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19. Wasserman et al. (W. Rubin, H. Steiner and J. Wasserman, *J. Chem. Soc.* **1949**, 3046.) have reported that some phenols accelerate the Diels-Alder reaction between *p*-benzoquinone and cyclopentadiene, but they suggest involvement of an electron transfer process.
20. The control experiments were conducted in parallel with the reactions given in the Table, using twice as many (compared to **8**) equivalents of *p*-nitrophenol or 4-nitro-3-(trifluoromethyl)phenol (American Tokyo Kasai). Reaction conditions were otherwise identical. The % product formation in the *p*-nitrophenol reactions for entries 1-11, respectively were 15, 46, 28, 36, 21, 60, 17, 10, 26, 30 and 16%. The % product formation with 4-nitro-3-(trifluoromethyl)phenol for entries 1, 3 and 7 was 13, 28 and 20%. Note that the difference in pK_a's is not reflected in their effect on reaction rate. Earlier qualitative studies (using the reaction between cyclopentadiene and cinnamaldehyde as the assay) leading to the choice of *p*-nitrophenol as the primary control indicated no correlation between the pK_a's of putative catalysts and their effectiveness: picric acid and acetic acid are inferior to *p*-nitrophenol as catalysts.
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