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Hydrogen Bonding Catalysis Operates by Charge Stabilization in Highly Polar Diels–Alder Reactions

Ruth Gordillo,[†] Travis Dudding,[‡] Christopher D. Anderson,[†] and K. N. Houk*,[†]

Department of Chemistry and Biochemistry, University of California,
Los Angeles, California 90095-1569, and Department of Chemistry, Brock University,
St. Catharines, Ontario L2S 3A1, Canada

houk@chem.ucla.edu

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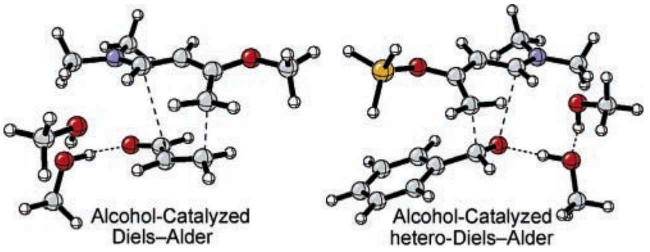
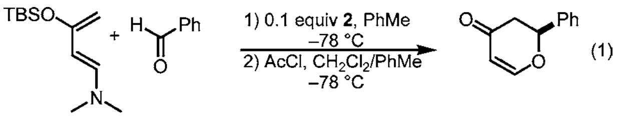
ABSTRACT



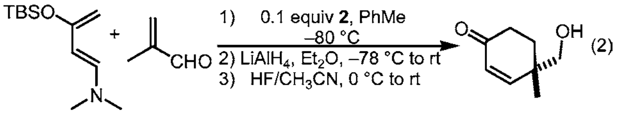
The alcohol-catalyzed Diels–Alder reactions of acrolein and benzaldehyde with Rawal's diene were evaluated with density functional theory (B3LYP/6-31G(d)). Several potential modes of catalysis with two methanol molecules were used to model catalysis by TADDOLs. In agreement with crystallographic data, cooperative catalysis with TADDOLs is predicted to be favorable.

Alcohols, ureas, and even water have been shown to accelerate Diels−Alder (DA) reactions.[1] Recently, Rawal and co-workers reported the hydrogen bond promoted hetero-Diels−Alder (hDA) reaction of unactivated ketones.[2] This initial publication was soon followed by many remarkable examples of asymmetric organocatalytic hDA and DA reactions mediated by chiral alcohols such as TADDOL **2** (eqs 1 and 2).[3,4]

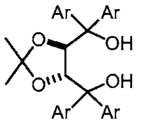
Several theoretical investigations have identified hydrogen bonding by solvent water as a source of acceleration in cycloaddition reactions.[1b−f] Domingo and co-workers reported a study of the solvent acceleration observed by Rawal and Huang in the hDA reaction between diene **5** and acetone demonstrating the role of hydrogen bonding interactions for the observed rate acceleration for reactions in $CHCl_3$ and MeOH.[5] More recently, Ding and co-workers reported a QM/



1 **3** (70%, >99% ee)



1 **4** (83%, 91% ee)



2 Ar = 1-naphthyl

[†] University of California, Los Angeles.

[‡] Brock University.

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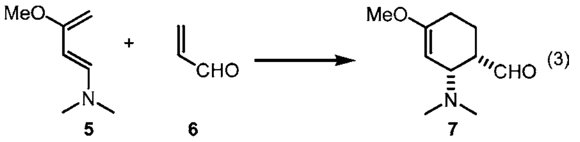
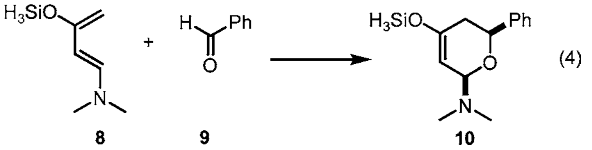
MM study of a TADDOL-catalyzed hDA reaction and proposed a model for stereoselectivity in this powerful reaction.[6]

We report a computational study of the alcohol- and diol-catalyzed Diels−Alder and hetero-Diels−Alder reactions of Rawal-type dienes **5** and **8** (eqs 3 and 4). This investigation provides an understanding of the rate acceleration provided by catalytic quantities of alcohols such as TADDOLs.



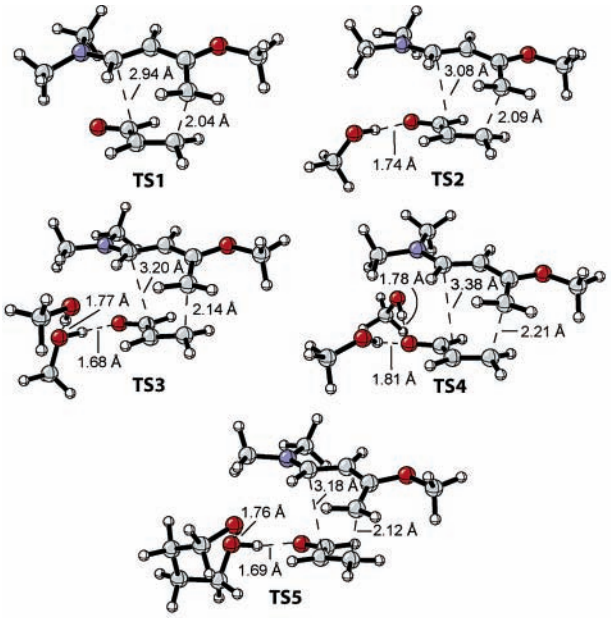
(3)



(4)

Computations were performed on the uncatalyzed reactions, the reactions catalyzed by a single methanol molecule, two methanol molecules, and 1,4-butanediol. All structures were computed using density functional theory (B3LYP)[7a−c] with the 6-31G(d)[7d−f] basis set as implemented in Gaussian 98 and 03.[7g−i]

Figure 1 shows the lowest energy transition structures for five of the DA reaction variations considered in this study. Catalysis by one methanol molecule lowers the activation energy of the cycloaddition reactions of diene **5** with acrolein by 4.3 kcal/mol (Table 1). Upon addition of a second molecule of MeOH, the activation energy is further reduced by 2.4 kcal/mol (cooperative mode, **TS3**). In the presence of 1,4-butanediol, the reaction barrier is reduced by 6.0 kcal/mol in the cooperative mode (**TS5**) relative to the uncatalyzed reaction. The bifurcated hydrogen bonding modes are predicted to be inferior to the corresponding cooperative modes, consistent with both experimental and theoretical studies of TADDOLs and TADDOL complexes.[3,6] It is noteworthy that the bifurcated modes of catalysis are also effective arrangements, as the bifurcated 2-MeOH model reduces the activation enthalpy of the DA reaction to 2.5 kcal/mol.



	separated reactants	starting complex	step 1 TS	intermediate	step 2 TS	product complex
uncatalyzed	0.0	---	11.2 (**TS1**)	n/a	n/a	−10.4
1–MeOH	8.7	0.0	6.9 (**TS2**)	n/a	n/a	−10.4
2–MeOH cooperative	19.4^{a} $(16.8)^{b}$	0.0^{a} $(0.0)^{b}$	4.5^{a} (**TS3**) $(1.9)^{b}$	-2.4^{a} $(-8.0)^{b}$	-1.9^{a} $(-6.3)^{b}$	-9.6^{a} $(-13.1)^{b}$
2–MeOH bifurcated	19.4^{a}	3.6^{a}	6.1^{a} (**TS4**)	-2.1^{a}	0.6^{a}	-9.4^{a}
1,4-butanediol cooperative	14.2^{c}	0.0^{c}	5.2^{c} (**TS5**)	-2.7^{c}	-1.6^{c}	-11.5^{c}
1,4-butanediol bifurcated	14.2^{c}	3.4^{c}	7.3^{c}	-0.6^{c}	2.2^{c}	-6.7^{c}

Figure 1. Lowest energy transition structures for the uncatalyzed and the alcohol-catalyzed Diels−Alder reaction between acrolein (**9**) and Rawal-type diene **8** and the relative enthalpies (kcal/mol) for the alcohol-catalyzed Diels−Alder reactions. [a] Relative to lowest energy 2-MeOH complex. [b] Relative to cooperative 2-MeOH complex and including solvation energy (PhMe). [c] Relative to lowest energy 1,4-butanediol complex.

The DA reactions mediated by two methanol molecules or 1,4-butanediol are predicted to proceed via zwitterionic intermediates in the gas phase.[8] These intermediates are short-lived and undergo cyclization through a low-barrier TS (H_{act} > 3 kcal/mol) to provide the cycloaddition product. For the model reaction mediated by two MeOH molecules in a cooperative arrangement, solvation free energy (PhMe) was calculated to better represent Rawal's reaction conditions.[9] In this case, solvation by PhMe reduces the activation enthalpy of the initial addition reaction by 2.6 kcal/mol and stabilizes the zwitterionic intermediate by 1.2 kcal/mol (Figure 1).

In all of the DA reactions, there is significant charge separation in both the transition structure (0.24−0.32 e) and in the intermediates (0.44−0.53 e) (see Supporting Information). In these cycloaddition reactions, the charge on oxygen increases significantly (ca. 0.1 e) in the transition structures.

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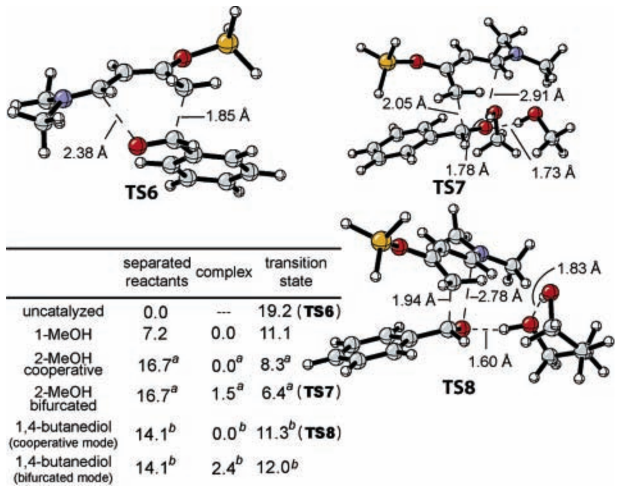
(8) For the 2-MeOH cooperative mode, a stable zwitterionic intermediate could not be located using MP2/6-31G(d). Bakalova, S. M.; Santos, A. G. *J. Org. Chem.* **2004**, *69*, 8475−8481. See Supporting Information for MP2 energies for 2-MeOH (cooperative mode) reaction.

(9) Solvation energies were calculated with CPCM/WAKS models: Takano, Y.; Houk, K. N. *J. Chem. Theory Comput.* **2005**, *1*, 70−77.

The increased charge on the carbonyl oxygen leads to increased hydrogen bonding in the TS, resulting in effective catalysis by hydrogen bond donors.



	separated reactants	complex	transition state
uncatalyzed	0.0	---	19.2 (**TS6**)
1-MeOH	7.2	0.0	11.1
2-MeOH cooperative	16.7^a	0.0^a	8.3^a
2-MeOH bifurcated	16.7^a	1.5^a	6.4^a (**TS7**)
1,4-butanediol (cooperative mode)	14.1^b	0.0^b	11.3^b (**TS8**)
1,4-butanediol (bifurcated mode)	14.1^b	2.4^b	12.0^b

Figure 2. Select hDA reaction transition states and table of relative enthalpies (kcal/mol) for the alcohol-catalyzed hDA reaction. ^{a} Relative to lowest energy 2-MeOH complex. ^{b} Relative to lowest energy 1,4-butanediol complex.

Figure 2 shows three of the calculated transition structures for the hDA reactions of diene **8** and benzaldehyde: uncatalyzed (**TS6**), catalysis by two methanol molecules in a cooperative mode (**TS7**), and catalysis by 1,4-butanediol (**TS8**). Under all of the modes of catalysis considered, the hDA reactions of diene **8** and benzaldehyde were concerted, asynchronous processes, consistent with the earlier investigations of Andrés and Domingo.[5]

All of the hetero-Diels−Alder reactions reported herein proceed through highly polarized transition states (charge separation of 0.20−0.35 e). Charge buildup on the carbonyl oxygen is more pronounced in the hDA reactions (ca. 0.2 e), resulting in increased hydrogen bonding in the TS. As in the case of the DA reaction, charge stabilization is a fundamental element of catalysis.

Two different models for TADDOL catalysis of the hDA reaction were evaluated: 2-MeOH and 1,4-butanediol. Both bifurcated and cooperative configurations were computed for each model of the catalyzed hDA reaction. In the case of the 1,4-butanediol catalyzed reaction, the bifurcated mode of catalysis is predicted to be less effective than the cooperative mode (Figure 2). Unlike the DA reaction, two hydrogen bonds to the carbonyl (bifurcated mode) lower the activation enthalpy more than the cooperative hydrogen bonding mode in the hDA reaction in the 2-MeOH model system. This suggests that catalysts that are capable of bifurcated hydrogen bonding modes, such as 1,8-biphenylenediol[10] and related compounds, may serve as a platform for extending alcohol catalysis to other polarized cycloaddition reactions.

In summary, hydrogen bond donors act by stabilizing charge in zwitterionic structures for polar Diels−Alder reactions. Large increases in charge polarization at the transition state of the reaction will lead to the highest levels of catalysis with hydrogen bond donors, as hydrogen bond donors induce only small perturbations in the charges of ground state complexes[11] (see Supporting Information). In most cases, cooperative modes of catalysis provide the largest reductions in activation enthalpy. The 1,4-butanediol model systems for catalysis by TADDOLs are consistent with a cooperative hydrogen bonding arrangement.[12] Studies aimed at further understanding the features that lead to high levels of stereoselectivity in Rawal's TADDOL-mediated DA and hDA reactions are under way.

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Note Added after ASAP Publication. In the version published ASAP on January 5, 2007, there were errors in references 1a, 1b, 4a, and 4b, these are correct in the version published ASAP on January 8, 2007.

Supporting Information Available: Cartesian coordinates and total electronic and zero-point vibrational energies of all reported structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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