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DFT Studies on Double Hydrogen Bond Catalysis of Reactions of Distinct Polarity

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The Diels–Alder cycloaddition and the enamine-aldol reactions catalyzed by double-site hydrogen-bond donors were computationally studied at the B3LYP and MP2/6-311++G** levels. The comparison of bifurcated and cooperative H-bonding activation of the electrophile in both reactions with 1,3-propanediol, 1,4-butanediol, glycolic acid and two molecules of methanol strongly suggests that the activation mode depends on the electronic features of the carbonyl oxygen atom in the H-bond acceptor. The bifurcated arrangement of the hydrogen-bond donors is predicted to be favoured as the polarity of the reaction increases. Consequently, the transition states of the Diels–Alder reaction are better stabilized by a cooperative interaction with the diols and those of the more polar enamine-aldol reaction by a bifurcated interaction.
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Introduction

The hydrogen-bond activation[1] of carbonyl compounds has emerged as a powerful tool in the enantioselective catalysis field.[2] Although efficient catalysts with different hydrogen-bond (H-bond) donor functionalities have appeared in recent years, the tremendous potential of this strategy has not yet been fully developed. In this regard, small molecules capable of double H-bond donation[3] are privileged species that benefit from increased H-bond strength and higher structural organization for a better transfer of chiral information. Besides nitrogen-based H-bond donors like thioureas,[4,5] amides,[6] guanidinium[7] and amidinium cations,[8] diols constitute another important group of H-bond donors. After seminal works in the 1980s involving the catalytic use of achiral biphenylenediols in nucleophilic additions to epoxides[9] and Diels–Alder reactions,[10] the introduction of chiral diols has dramatically expanded the importance of diol-based catalysts. For instance, TADDOL [(–)-*trans*-α,α′-(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)][11] and BAMOL [1,1′-biaryl-2,2′-bis(diarylmethanol)][12] have succeeded in effectively catalyzing very different organic transformations such as the Mukaiyama or Diels–Alder reactions. Whilst there is little doubt about the participation of ureas and thioureas as double-point H-bond promoters,[13] the higher flexibility of diols allows them to act as single- or double-point activators.[14] In the single-point activation mode (cooperative activation, **A** in Table 1), the carbonyl oxygen atom binds to one OH group of the diol, whose acidity is enhanced by an intramolecular H-bond with the second OH group. In the double-point activation pattern (bifurcated activation, **B** in Table 1) two intermolecular H-bonds are formed between the diol and the two lone pairs of the oxygen atom. On the basis of crystallographic data, the interaction of diols with carbonyl compounds has been proposed to fit better with the single-point pattern. For example, the vast majority of the X-ray crystal structures obtained for complexes between TADDOL and aldehydes[11f,12,15] present a cooperative arrangement on TADDOL. The known fact that 1,4-diols form an intramolecular H-bond[11b,16] also supports this hypothesis. By analogy, reactions involving diols have been ascribed to the single-point activation pattern. However, despite its inherent interest, little is known about the precise nature of the H-bonding interaction between substrates and diols during transition states.[17] We were intrigued by the possibility that the binding mode in the transition state might not resemble the pattern found by X-ray for ground states. The central question is whether more negative oxygen atoms (like those in transition states involving carbonyl compounds) might prefer to form two H-bonds with the catalyst for a better charge stabilization. Being so, reactions with different polar character might show different activation patterns. Indeed, one case was reported in which two molecules of methanol activate the relatively less-polar Diels–Alder reaction of cyclopentadiene and acrolein by cooperative H-bonding (type **A**) and the more-polar hetero-Diels–Alder reaction of benzaldehyde by bifurcated H-bonding (type **B**).[18] Thus, the question still remains open. Herein, we report a computational study aimed at getting a deeper understanding of the hydrogen-bonding activation

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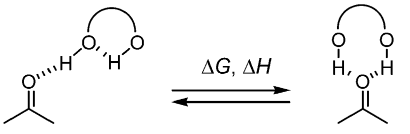
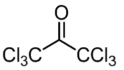
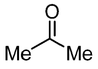
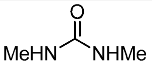
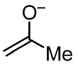
of carbonyl compounds with diols during the transitionstates of the apolar (all carbon) Diels–Alder reaction and the polar aldol reaction.

Table 1. Energy differences between cooperative (**A**) and bifurcated (**B**) H-bond complexes of compounds **1**–**4** with different alcohols, computed at the B3LYP/6-311++G** level, and single-point values at MP2/6-311++G** (in parenthesis).



A **B**

	 **1**	 **2**	 **3**	 **4**
Charge on O[a]	–0.45	–0.54	–0.65	–0.80
		ΔH[b]		
1,3-Propanediol	2.2 (0.6)[c]	1.5	0.3	–4.3 (–4.8)
1,4-Butanediol	only **A**	3.2	2.2	–1.6
Methanol	5.5 (4.4)	3.0	2.5	–2.3 (–2.8)
		ΔG[b]		
1,3-Propanediol	3.4 (1.7)	1.8	1.7	–1.9 (–2.4)
1,4-Butanediol	only **A**	2.6	3.1	–0.5
Methanol	3.2 (2.0)	1.7	1.6	–1.8 (–2.3)

[a] Charge in e. [b] Energies in kcal/mol computed as $\Delta H = H_B - H_A$ or $\Delta G = G_B - G_A$. Positive values reflect preferred formation of type **A** complex; negative values indicate formation of type **B** complex. [c] Values in parentheses correspond to single-point MP2/6-311++G**//B3LYP/6-311++G** energies.

Computational Methods

All structures were optimized by using the B3LYP[19] functional and the 6-311++G** basis set, as implemented in Gaussian 03,[20] including polarization functions for a better description of hydrogen bonds involved in the reactions. The DFT geometry optimization performance was evaluated by comparison of the X-ray structure and the computed structure[21] of a TADDOL–benzaldehyde complex.[11f] The energies reported in this work include the zero-point vibrational energy corrections (ZPVE) and are not scaled. To get more accurate energies, single-point calculations were performed at MP2(fc)/6-311++G**//B3LYP/6-311++G** + ΔZPVE(B3LYP) on some of the previously DFT-optimized structures.[22] All energy minima and transition states were characterized by frequency analysis in order to verify that they have the right number of negative eigenvalues. The intrinsic reaction coordinate (IRC)[23] was followed to verify the energy profiles connecting each transition state with the correct local minima. Atomic charges were calculated within the natural bond orbital (NBO) analysis.[24]

Results and Discussion

Initial insight on our question came by computing complexation energies between several electronically different symmetrical carbonyl compounds **1**–**3** and double-site H-bond donors, that is, 1,3-propanediol, 1,4-butanediol and two molecules of methanol[25] (Table 1). Compounds **1**–**3** were chosen as representative carbonyl compounds for two reasons: (a) they represent carbonyl species with different electronic properties by introduction of electron-poor and electron-rich substituents and (b) they are C_2-symmetrical, simplifying the number of conformations to be calculated in their interaction with the alcohols. Enolate **4**, derived from acetone, was also studied due to its much higher negative charge at the oxygen atom.

In agreement with the mentioned crystallographic data, cooperative activation mode **A** is preferred for neutral carbonyl compounds **1**–**3**, but this preference clearly diminishes as the negative charge on oxygen increases. In fact, the presence of two electron-withdrawing substituents (–CCl_3) in **1** lowers the negative charge at the oxygen atom to –0.45 e and is enough to induce the preferential formation of **A**-type complexes by 2–5 kcal/mol. Noteworthy, in the presence of butanediol, complex **B** could not be located and converged to the corresponding **A**-type complex during optimization. Acetone (**2**) and tetramethylurea (**3**), which bear an increasing negative oxygen atom, show a decreasing preference for cooperative complexation (**A** type).

Most interestingly, the preference is reversed for anionic enolate **4**, which forms a **B**-type complex that is 1.6–4.3 kcal/mol stronger than type **A**, in agreement with the large negative charge computed for its oxygen atom (–0.80 e). This behaviour must be mostly based on electronic factors rather than structural requirements on the diol, as the same tendency is observed with two molecules of the rotational more flexible methanol (Table 1).

The inclusion of the entropic cost, which is higher in type **B** complexation, might have an influence in the binding Gibbs energy, favouring mode **A**. In fact, all ΔG values are slightly more positive (or less negative) than ΔH values (except for methanol). Nevertheless, this difference does not have any influence on the binding preference trend, which is still mode **A** for electron-poor **1**, and mode **B** for electron-rich **4**. The results are also independent of the computational method used. Single-point energies at the MP2(fc)/6-311++G**//B3LYP/6-311++G** level show a similar binding trend (Table 1), although with a higher preference for bifurcated modes in all cases. Indeed, the positive values reflecting the preference for cooperative mode **A** with ketone **1** decrease (propanediol, 2.2 to 0.6 kcal/mol; methanol, 5.5 to 4.4 kcal/mol), whilst negative values found for enolate **4** increase (propanediol, 4.3 to 4.8 kcal/mol; methanol, 2.3 to 2.8 kcal/mol).

Significant differences are found in the H-bonding distances (and therefore in the H-bonding strength) of each complex, which has crucial implications on the relative stability of the different complexes. The geometries of the complexes with two molecules of methanol are shown in Figure 1. The electron-poorest oxygen atom (compound **1**) behaves as a very bad H-bond acceptor and forms one weak H-bond with methanol (Figure 1) in the cooperative mode (2.12 Å). Two even weaker H-bonds (2.31 Å) are formed when **1** binds to two molecules of methanol simultaneously, giving rise to a very loose, high-energy complex (bifurcated mode). Thus, cooperative mode **A**, which bears an H-bond of standard length (1.87 Å) between the two molecules of methanol, is preferred by more than 5 kcal/mol. The opposite is true for enolate **4**. The high negative charge on the oxygen atom is enough to form two strong, tight H-bonds (1.65 and 1.67 Å) with methanol in mode **B**, forming a strong bifurcated complex, which is preferred by 2.3 kcal/mol to the cooperative one. Similar geometries and H-bond lengths were computed for propanediol and butanediol, in agreement with the energy values shown in Table 1.

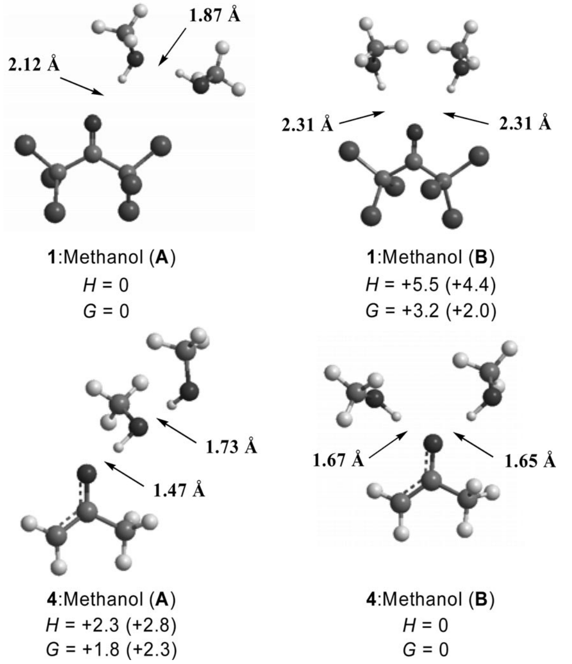


Figure 1. Cooperative (**A**) and bifurcated (**B**) complexes of two molecules of methanol with compounds **1** and **4**. Values in parentheses correspond to MP2/6-311++G**//B3LYP/6-311++G** single-point energies.

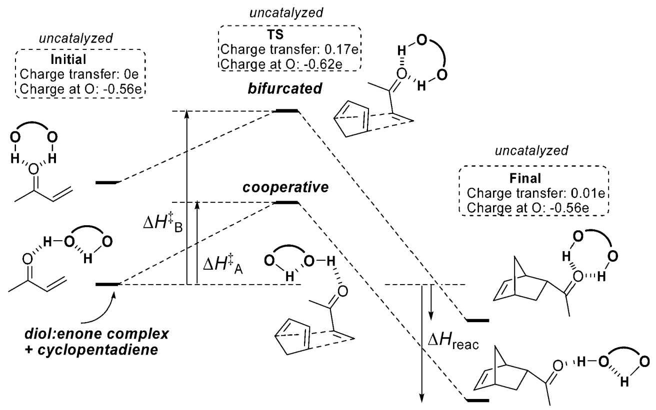
We hypothesized that a similar reasoning would apply for reactions with distinct polar character, because the main difference between polar and apolar reactions resides in the amount of charge transferred from the nucleophilic to the electrophilic counterpart and, hence, in the amount of negative charge developing at the oxygen atom during the transition state. To this end, we explored quantum mechanically (a) the Diels–Alder cycloaddition between cyclopentadiene (CP) and methyl vinyl ketone (MVK)[26] and (b) the aldol reaction between an enamine (2-dimethylaminopropene) and acetaldehyde,[27] two reactions that can be considered as representative examples of apolar and polar reactions, respectively. According to NBO analysis of the uncatalyzed reactions, the transition state of the apolar Diels–Alder reaction presents a charge transfer from CP to MVK of only 0.17 e, whilst a strong charge transfer of 0.57 e was computed for the enamine-aldol reaction. The electronic differences between both uncatalyzed reactions were also revealed by the computed charge of the oxygen atom. First, a low and steady charge is found at the oxygen atom along the Diels–Alder reaction coordinate, –0.56, –0.62 and –0.56 e for MVK reactant, transition state and final adduct, respectively (Table 2), whereas in striking contrast, an increasing strong negative charge at the oxygen atom is observed in the enamine-aldol reaction, –0.53, –0.78 and –0.92 e for aldehyde, TS and product, respectively (Table 3).

In view of the charge values, the enamine-aldol reaction must be significantly more sensitive to H-bond activation than the Diels–Alder cycloaddition. Concerning the activation mode, carbonyl-like behaviour for the Diels–Alder reaction and alkoxide-like behaviour for the aldol reaction are to be expected. The comparison of their activation parameters with different H-bond donors, that is, methanol, 1,3-propanediol, 1,4-butanediol and glycolic acid,[28] is clarifying (Tables 2 and 3).

Diels–Alder Reaction

The noncatalyzed reaction between CP and MVK presents an activation enthalpy of 18.7 kcal/mol (Table 2, En-

Table 2. Computed enthalpies (ΔH) and Gibbs energies (ΔG) for the Diels–Alder reaction catalyzed by H-bond donors.[a]

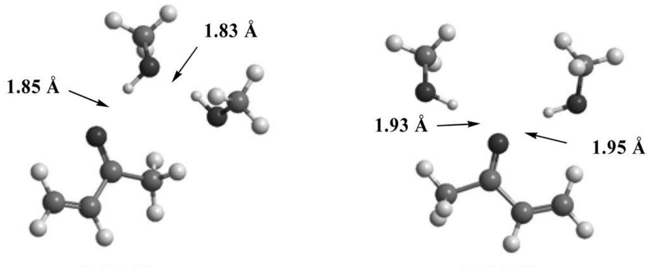


Entry		$\Delta H^{‡[b]}$		ΔH_{reac}	
		cooper. (**A**)	bifurc. (**B**)	**A**	**B**
1	none	18.7		–9.9	
2	propanediol	16.1	18.2	–9.7	–9.5
3	butanediol	13.8	15.5	–10.1	–8.9
4	methanol	14.9	16.5	–10.1	–7.1
5	glycolic acid	14.5	20.7	–10.1	–3.1
		$\Delta G^{‡[b]}$		ΔG_{reac}	
6	none	32.3		4.6	
7	propanediol	31.5 (13.8)[c]	34.0 (16.5)	5.7	6.4
8	butanediol	28.7 (13.0)	31.3 (15.3)	5.3	7.1
9	methanol	29.7 (12.1)	30.9 (13.8)	4.9	7.0
10	glycolic acid	29.4	35.2	5.0	11.2

[a] Charge-transfer and charge at oxygen values refer to the uncatalyzed reaction. [b] Energies in kcal/mol computed at B3LYP/6-311++G**. [c] Values in parentheses correspond to single-point MP2/6-311++G** energies.

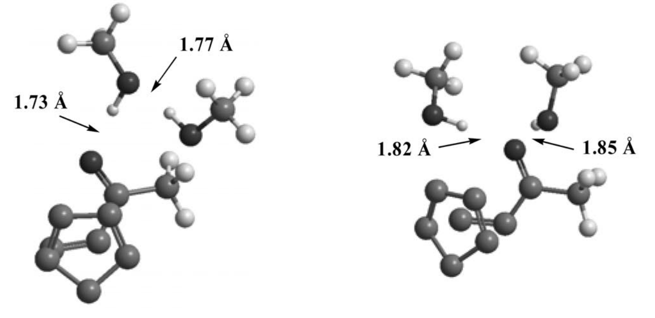
try 1) and an activation Gibbs energy of 32.3 kcal/mol (Table 2, Entry 6).[29] The interaction with alcohols slightly lowers the activation barriers to $\Delta H^{\ddagger}$ = 14–16 kcal/mol (Table 2, Entries 2–4) and $\Delta G^{\ddagger}$ = 29–31 kcal/mol (Table 2, Entries 7–9). Glycolic acid, which is a better H-bond donor than a diol, is not a better reaction promoter (Table 2, Entry 5).

Most interestingly, the cooperative activation mode is preferred in all cases, with an energy difference in favour of mode **A** over **B** of ca. 1.5–2 kcal/mol for diols (Table 2, Entries 2–4) and higher for glycolic acid (6.2 kcal/mol; Table 2, Entry 5). The coordination preference for cooperative binding remains unaltered throughout the reaction. For instance, $\Delta\Delta H$ values of 1.5, 1.7 and 1.2 kcal/mol in favour of mode **A** were computed for the binding of 1,4-butanediol with MVK, the transition state and the product, respectively. The final adducts lie ca. 10 kcal/mol lower in energy than the starting reactant regardless of the H-bond donor.



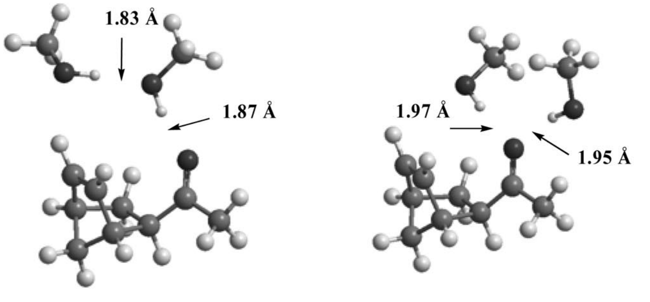
A (MVK)
H = 0
G = 0

B (MVK)
H = 2.6
G = 1.4



A (Transition State)
$\Delta H^{\ddagger}$ = 14.9
$\Delta G^{\ddagger}$ = 29.7 (12.1)

B (Transition State)
$\Delta H^{\ddagger}$ = 16.5
$\Delta G^{\ddagger}$ = 30.9 (13.8)



A (Final Adduct)
ΔH_R = -10.1
ΔG_R = 4.9

B (Final Adduct)
ΔH_R = -7.1
ΔG_R = 7.0

Figure 2. Cooperative (**A**) and bifurcated (**B**) complexes of methyl vinyl ketone, Diels–Alder transition states (CP+MVK) and the final adduct with two molecules of methanol. Some hydrogen atoms in the transition states are omitted for clarity. Values in parentheses correspond to MP2/6-311++G**//B3LYP/6-311++G** single-point energies.

The Gibbs energy values show a similar tendency (Table 2, Entries 6–10), which is also independent of the calculation method used. In our particular case, the MP2 method predicts in general lower absolute activation barriers than the DFT method, but the relative values between both activation modes are not altered. For example, the cooperative transition state **A** lies 2.5 kcal/mol (B3LYP) or 2.7 kcal/mol (MP2) lower in Gibbs energy than **B** in the presence of propanediol and 2.6 kcal/mol (B3LYP) or 2.3 kcal/mol in the presence of butanediol.

The lengths of the corresponding H-bonds are in agreement with the energy values. MVK prefers to form a single H-bond of standard O–H···O length (1.85 Å) with methanol. The other H-bond formed between the two molecules of methanol has a similar length (1.83 Å; mode **A**, Figure 2). Thus, both are stronger than those found in complex **B** (1.93 and 1.95 Å), meaning that the oxygen atom of MVK has only enough negative charge to form one regular H-bond (preferred **A** complex) or two weak ones (mode **B**, 2.6 kcal/mol higher in energy).

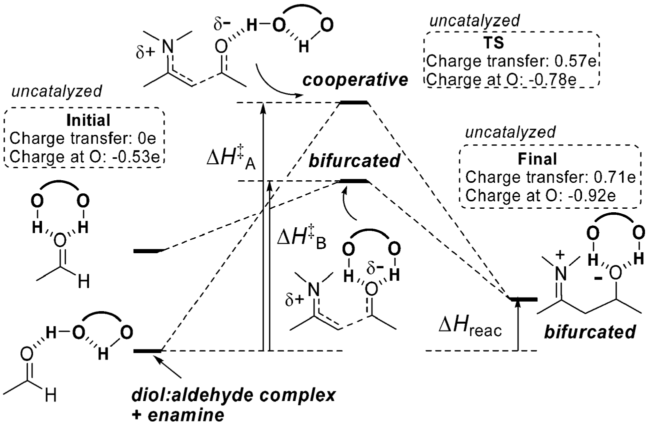
Along the reaction coordinate, the strength of the H-bonds slightly increases during the transition state (0.1 Å in average) and weakens back to the initial values within the final adducts, which is in agreement with the aforementioned electronic features of the carbonyl oxygen in the Diels–Alder reaction. Nevertheless, the relative distance variations between the cooperative and bifurcated complexes remains unchanged, and the strongest H-bonds are always those computed for mode **A**, which are ≈0.1 Å shorter in general than in mode **B**.

Enamine-Aldol Reaction

A complete different scenario was found for the highly polar enamine-aldol reaction. The reaction is very sensitive to H-bond activation. The activation enthalpy for the non-catalyzed reaction (19.0 kcal/mol; Table 3, Entry 1) is significantly reduced to 7.4–9.9 kcal/mol in the presence of alcohols (Table 3, Entries 2–4) and to 7.0 kcal/mol for glycolic acid (Table 3, Entry 5). Noteworthy, *the bifurcated arrangement of the diols or methanol reduces the activation barriers more efficiently than the cooperative mode*, favouring mode **B** over **A** by 0.4–1.9 kcal/mol (Table 3, Entries 2–4). The need for a strong hydrogen bond stabilization of the highly charged oxygen atom in the alkoxide-like transition state seems to be the reason for the prevalence of **B**-type activation. It is also remarkable that the energy difference in favour of the bifurcated binding mode (**B**) increases along the reaction coordinate and becomes maximal in the zwitterionic product[30] after the transition state. This finding is in agreement with the high negative charge developed at its oxygen atom (–0.92 e). We only could locate interaction **B** between the zwitterion and the diols, whereas mode

A spontaneously converged to **B** during optimization. Once again, MP2 single-point energies show a similar tendency, favouring the bifurcated arrangement by 2.5 (propanediol), 1.3 (butanediol) and 0.7 kcal/mol (methanol).

Table 3. Computed enthalpies (ΔH) and Gibbs energies (ΔG) for the enamine-aldol reaction catalyzed by H-bond donors.[a]

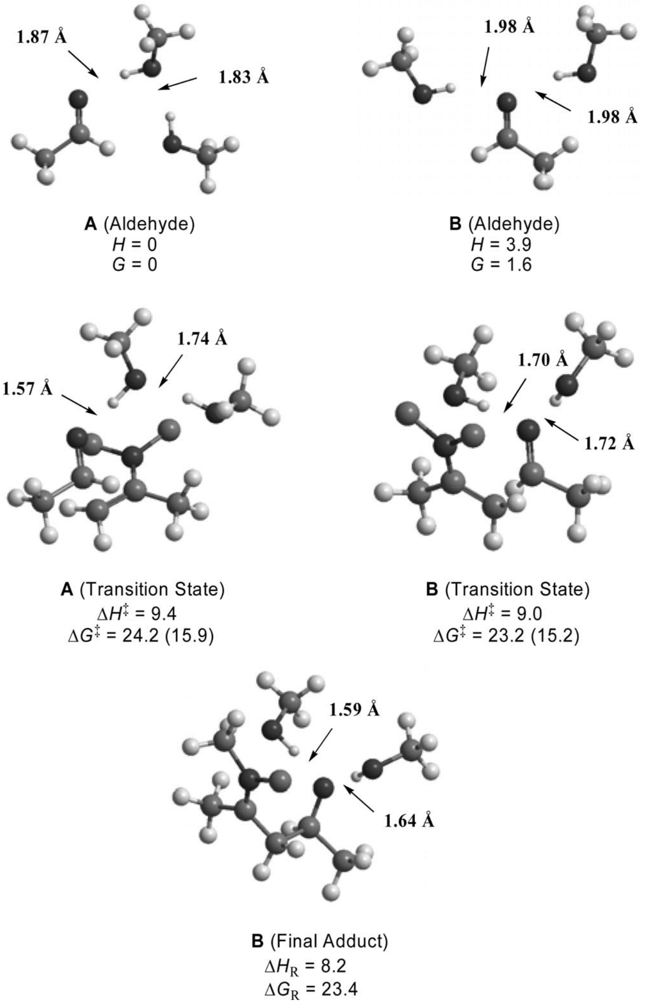


Entry		$\Delta H^{‡[b]}$		ΔH_{reac}
		cooper. (**A**)	bifurc. (**B**)	only **B**
1	none	19.0		
2	propanediol	11.0	9.9	9.5
3	butanediol	9.3	7.4	7.3
4	methanol	9.4	9.0	8.2
5	glycolic acid	7.0	10.3	–2.6
		$\Delta G^{‡[b]}$		ΔG_{reac}
6	none	29.1		
7	propanediol	24.8 (18.0)[c]	23.9 (15.5)	23.8
8	butanediol	26.2 (16.6)	24.6 (15.3)	25.1
9	methanol	24.2 (15.9)	23.2 (15.2)	23.4
10	glycolic acid	22.0	26.4	14.5

[a] Charge-transfer and charge at oxygen values refer to the uncatalyzed reaction. [b] Energies in kcal/mol computed at B3LYP/6-311++G**. [c] Values in parentheses correspond to single-point MP2/6-311++G**//B3LYP/6-311++G**+ZPVE energies.

In contrast, the stronger H-bond donor carboxylic acid functionality present in the glycolic acid seems to be enough to stabilize the negative charge by a single H-bond, and cooperative activation is preferred by 3.3 kcal/mol. Nonetheless, the preference for mode **A** is lower in the aldol reaction that that in the Diels–Alder reaction ($\Delta\Delta H^{‡}$ = 6.2 kcal/mol; Table 2, Entry 5).

The H-bonding pattern found in the enamine-aldol reaction (Figure 3) drastically differs from the previous one in the Diels–Alder reaction. Whereas the initial H-bond lengths between methanol and acetaldehyde are closely related to those of MVK or acetone, the higher negative charge at the oxygen atom during the transition state induces the formation of tighter complexes, which reproduce the geometrical features of complexes with enolate **4**. Thus, short H-bond lengths (1.70 and 1.72 Å) are computed for the bifurcated complex (Figure 3), similar to those computed for the complex between methanol and enolate **4** (1.65 and 1.67 Å, Figure 1), as an indication of a large H-bond activation of the reaction, and a preference for the **B**-type complex. This effect is even more dramatic in the final adduct, which forms a tight bifurcated complex with very short H···OH distances of 1.59 and 1.64 Å. Two H-bonds seem to be necessary at this point to stabilize the high negative charge at the O atom. The other alcohols studied, propanediol and butanediol, show similar geometrical features.



A (Aldehyde)
H = 0
G = 0

B (Aldehyde)
H = 3.9
G = 1.6

A (Transition State)
$\Delta H^{‡}$ = 9.4
$\Delta G^{‡}$ = 24.2 (15.9)

B (Transition State)
$\Delta H^{‡}$ = 9.0
$\Delta G^{‡}$ = 23.2 (15.2)

B (Final Adduct)
ΔH_R = 8.2
ΔG_R = 23.4

Figure 3. Cooperative (**A**) and bifurcated (**B**) complexes of acetaldehyde, aldol transition states (enamine + aldehyde) and the final adduct with two molecules of methanol. Some hydrogen atoms in the transition states are omitted for clarity. Values in parentheses correspond to MP2/6-311++G**//B3LYP/6-311++G** single-point energies.

Conclusions

Our calculations suggest that the complexation mode of diols with carbonyl compounds strongly depends on the electronic character of the oxygen atom to which they bind; low-charge oxygen atoms (Diels–Alder reaction) prefer a cooperative interaction, whereas highly negative ones (enamine-aldol reaction) are better stabilized by bifurcated H-bonds. Thus, the mode of interaction found by X-ray analysis of ground-state carbonyl compounds does not automatically apply to the binding mode of polarized transition states. As a result of the structural differences between both activation types, these observations might be helpful to design more efficient catalysts for both polar and apolar reactions, specially because the bifurcated model removes the conformational ambiguity associated with the single-point binding mode, which is an attractive feature from the perspective of asymmetric catalysis.

Supporting Information (see footnote on the first page of this article): Cartesian coordinates and absolute energies of all reported structures.

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