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Mechanistic investigations in α-hydroxycarbonyls reduction by BH_4^-

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BH_4^-, a well-known and widely used reducing agent for carbonyl compounds, has been reported to have the ability to participate in dihydrogen bonding, an interaction with applications in catalysis, stereoselectivity and crystal engineering. Specifically, α-hydroxycarbonyls are activated for reduction by dihydrogen bonding that occurs between BH_4^- and hydroxyl group. We explored the effect of the interaction on the mechanism of these reactions by examining their activation parameters. We found that dihydrogen bonding activates α-hydroxycyclopentanone for reduction with NBu_4BH_4 by lowering the activation enthalpy by 6.6 kcal/mol. While the activation entropy is a significant component of the barrier, the changes resulting from the occurrence of dihydrogen bonding are manifested predominantly in the enthalpy term. Computational studies suggest that, while internal hydrogen bonding is allowed by the flexibility of the carbon backbone, that interaction is outweighed by dihydrogen bonding once BH_4^- is present in the system. Experimentally, a red shift of the hydroxyl frequency is observed upon addition of BH_4^- to the reaction mixture, suggesting a dihydrogen bonding interaction. The flexibility of the substrate's skeleton or the selectivity of the hydride sites in BH_4^- does not account for the lack of directing effect of the dihydrogen bonding. When a substrate with a rigid naphthalene backbone moiety, 2-hydroxyacenaphthylen-1(2H)-one, is reduced, the stereochemical outcome is very similar to the one corresponding to the α-hydroxycyclopentanone. Copyright © 2012 John Wiley & Sons, Ltd.
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Keywords: dihydrogen bonding; carbonyl; activation; rate

INTRODUCTION

Borohydrides have been widely used reducing agents since their discovery more than half a century ago.[1] Their mild reducing ability, chemo- and stereoselectivity, and ease of use (a typical reaction involves treatment of the carbonyl compound with $NaBH_4$ in a protic solvent, followed by acid or basic work-up to yield the corresponding alcohol) are attractive for organic synthesis. Since the report of their first reduction reaction,[2] several mechanistic studies have appeared, but the intimate molecular details remain uncertain. The complexity of the problem arises from the availability of four hydride sites, all of which ultimately react, though there is general agreement that the rate determining step (RDS) is the transfer of the first hydride.[3] Kinetic studies of cyclic ketone reductions by $NaBH_4$ concluded that the rate law was first order with respect to both ketone and borohydride in an aprotic solvent. On the other hand, the reaction was accelerated in the presence of an alcohol (isopropanol) leading to rate law expressions with a 1.5 order in the alcohol.[4] Based on this latter experimental finding and the fact that the alkoxyborate product contained alcohol groups belonging to the solvent, in 1979, Wigfield proposed that the transition state should be product-like, not involve the borohydride's counterion and contain a solvent molecule.[5] Subsequent ab initio gas phase calculations at the SCF/3-21G* level, by Eisenstein *et al.* suggested that indeed the transition state is cyclic with the C–H bond almost completely formed while the BH_3 fragment was flat and in close proximity to the carbonyl oxygen, but with the B–O bond not completely formed.[6] Moreover, incorporation of a water molecule lowered the calculated activation barrier from 32.5 kcal/mol (Fig. 1A) to 17.5 kcal/mol (Fig. 1B), presumably due to stabilization of the carbonyl oxygen's developing charge via hydrogen bonding. At the same time, the geometry was essentially unaffected by the water's presence: the distance between B and the transferred hydride remained constant, while the B–O distance increased by 0.1 Å as the carbonyl oxygen was hydrogen bonded to the water molecule. Furthermore, experimental studies aimed at elucidating the reaction's thermochemistry found that formaldehyde could not be reduced in the gas phase by BH_4^- ion alone in the absence of a cation or solvent.[7] While many research groups accepted the transition state geometry proposed by Wigfield, several experimental studies showed that when the reducing agent is $NaBH_4$, sodium plays a role in the reaction's mechanism.[8,9] Replacement of sodium with a non coordinating cation such as tetrabutyl ammonium significantly slows the reaction rate.[10] Recent density functional calculations by Tomoda *et al.*, at the B3LYP/6-31 + G* level on acetone reduction with $NaBH_4$, showed that the metal borohydride counterion complexed the carbonyl oxygen at the transition state while the product-like geometry was preserved (see Fig. 2A). With respect to geometry, the main differences between the transition

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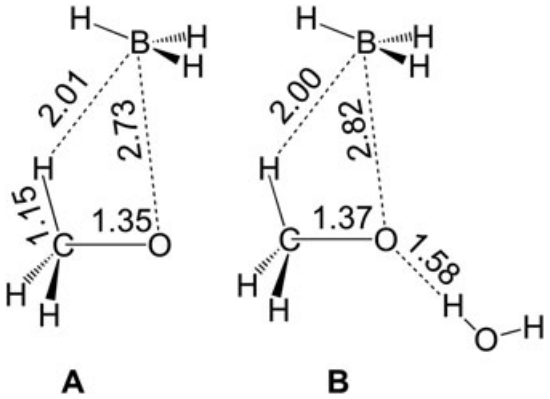


Figure 1. Transition state geometries for formaldehyde reduction by BH_4^- calculated by Eisenstein *et al.*

states calculated by Tomoda and by Eisenstein are in the boron-transferred hydride (B-H_{trans}) distances, which were 2.01 Å and 2.22 Å, respectively. These changes are due presumably to a preference by the carbonyl's oxygen for the Na^+ over the neutral BH_3. Moreover, incorporation of methanol molecules (Fig. 2B) in an attempt to account for the solvent once again lowered the barrier from 35.2 kcal/mol to 10.9 kcal/mol.[11] Coordination around the sodium cation was modeled as three methanol molecules and the carbonyl's oxygen atom. By contrast with the Eisenstein model, where the presence of water did not affect the B-H_{trans} distance, inclusion of methanol molecules in the Tomoda model led to elongated carbonyl O-Na and B-H_{trans} contacts. Meanwhile, B-Na distance was essentially unaffected (see Fig. 2B) suggesting that the involvement of Na in the reaction was reduced due to its complexation with methanol. It is worth mentioning that the theoretical value for the activation energy obtained for the solution reaction falls within the range of experimental activation barriers, 5.4–11.1 kcal/mol, determined for a series of cyclohexanone reductions by $NaBH_4$ in isopropanol.[5]

Until recently, although interactions of the carbonyl's oxygen with either counter cations or protic solvents had been explored, the possibility of a dihydrogen bond between BH_4^- and the hydroxyl group of a solvent such as isopropanol was not considered.[12] One possible reason for this omission is the relative novelty of dihydrogen bonding, compared to the long-known reduction of carbonyl compounds by borohydrides. The term 'dihydrogen bonding' refers to interactions between traditional proton donors and hydrides of elements less electronegative than hydrogen. Though hints had appeared earlier, these associations were only explicitly recognized in the literature in the mid 90s. In the intervening years, their structures and association energies have been explored, and their importance in reactivity and selectivity in solution and the solid state has been demonstrated.[12–19] Crabtree and Yao showed that an intramolecular Ir-H. . .H-O dihydrogen bond is responsible for the selective imination of a carbonyl functionality in an iridium complex, $[IrH_2(\eta^2\text{-}C_5H_4NCHO\text{-}N,O)(PPh_3)_2]^+$ in the presence of an equimolar mixture of 2-aminophenol and 4-aminophenol.[17] In 1999, Gatling and Jackson reported that the presence of a hydroxyl group vicinal to a ketone accelerates the reaction and controls the stereochemistry. Specifically, in chlorinated hydrocarbon solvents, half-lives for reduction of 2-hydroxycycloalkanones by tetrabutylammonium borohydride (NBu_4BH_4) were found to be 100 times faster than for the corresponding simple cycloalkanones. Moreover, the isolated products were found to be almost exclusively *trans* diols indicating that the hydride was delivered from the OH substituted face of the substrate.[18] It was hypothesized that a dihydrogen bonded complex was formed prior to reduction and retained through the hydride transfer process. As in the older analyses of carbonyl reduction by the BH_4^- ion, the RDS was taken to be the transfer of the first hydride, Scheme 1. More recently, based on the observed rate acceleration in the presence of water, Lau *et al.* suggested a central role for an intermediate dihydrogen bonded complex TpRu(PPh_3)(H_2O)H (Tp = hydro(trispyrazolyl)borato) in the Ruthenium-catalyzed hydrogenation of CO_2 to formic acid in THF.[19] Morris and coworkers proposed an alcohol-assisted bifunctional mechanism for H_2 hydrogenation of ketones catalyzed by the [RuCp(C-NH_2)py]PF_6 (Cp = pentamethylcyclopentadienyl, C-NH_2 = N-heterocyclic carbene with a tethered primary amine donor, py = pyridine). Based on both experimental and computational data, they suggested that the dihydrogen bonding interaction facilitates heterolytic splitting of the H_2 molecule followed by proton/hydride transfer to the ketone.[20]

We set out to explore the proposed guiding effects of dihydrogen bonding on the mechanism of reduction of 2-hydroxycycloalkanones with tetrabutylammonium borohydride by examining their rates and activation parameters. Via comparisons to results previously determined in protic solvents, we hoped to gain insight into the relationship between the nature of the transition state and the stereochemical outcome of this reaction. Among the 2-hydroxycarbonyl substrates investigated by Gatling

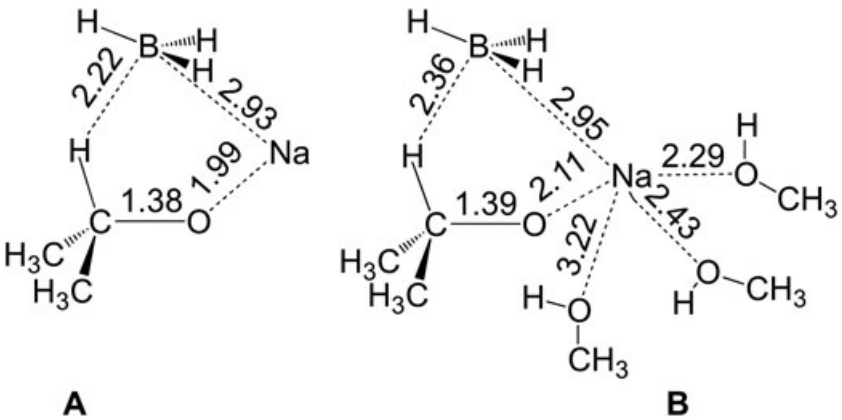
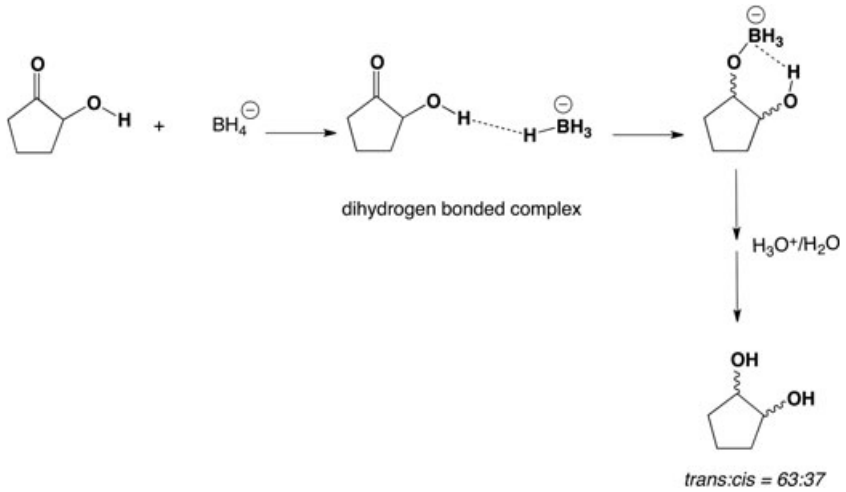


Figure 2. Transition state geometries for acetone reduction by $NaBH_4^-$ calculated by Tomoda *et al.*



Scheme 1. Reduction of 2-hydroxycyclopentanone by BH_4^-

and Jackson earlier, 2-hydroxycyclopentanone was deemed to be the most appealing due to the previous findings that its reduction manifested both activation and stereocontrol, and that it was more stable (and hence easy to work with) than the more rigid but more delicate 2-hydroxycyclobutanone.

Direct analysis (i.e. no derivatization or isolation steps) of the reaction mixture for reduction of 2-hydroxycyclopentanone by NBu_4BH_4 in CH_2Cl_2 at ambient temperature led to a 63:37 *trans*:*cis* ratio of diols, in stark contrast with the earlier 99.7:0.3 *trans:cis* ratio reported by Gatling and Jackson.[18] This remarkable departure from the previous results reflects the high hydrolytic stability of borate esters of cis cyclopentanediol relative to their trans isomers. While we now know that this earlier work from our labs fails in terms of stereocontrol in the case of 2-hydroxycyclopentanone, it does offer a methodology to preferentially isolate one of the isomers, the trans diol, albeit in modest yield.

In the present reexamination, we concentrated our attention on the reaction kinetics and on exploring the cause for the diminished stereocontrol, specifically the role played by the flexibility of the ketone's backbone and the competition between classical hydrogen bonds and dihydrogen bonding. We report here the experimental activation parameters for the above and a related reaction, as well as a rationale for the stereochemical distribution based on both experimental and computational efforts.

METHODOLOGY

Experimental

Materials

Ketones studied were synthesized based on published procedures.[18,21] Reagents were purchased from Sigma-Aldrich, verified for purity by NMR and IR and if needed, purified. Solvents were also purchased from Sigma-Aldrich; dichloromethane (solvent grade) was dried over P_2O_5 but 1,2-dichlorobenzene (1,2-DCB), packaged in Sure Seal bottles, was used as purchased after its dryness was verified by IR spectrophotometry.

Kinetic measurements

The reduction of 2-hydroxycyclopentanone was monitored at different temperatures over a range of 40 K by solution IR spectroscopy using a REACT IR MP Mobile spectrophotometer. The concentrations of ketone and borohydride in 1,2-DCB were 0.1 and 0.4 M, respectively, to ensure an excess of the reducing agent at all times. The progress of the reaction was followed via changes in the ketone concentration based on the calibrated area of the carbonyl peak (1748.6 cm^{-1}). The borohydride concentration was determined indirectly by difference based on the reaction equation and conversion.

Product distribution analysis

Reduction of 2-hydroxycyclopentanone by NBu_4BH_4. Determinations were conducted via HPLC chromatography using an Aminex HPX-87H column and 5 mM H_2SO_4 mobile phase with a flow rate of 0.6 ml/min and UV (210 nm) detection.

Reduction of 2-hydroxyacenaphthylen-1(2H)-one by NBu_4BH_4. Determinations employed HPLC chromatography on an Agilent C18 RPLC column using a modified published procedure:[20] a 40 min methanol/water gradient from 30/70 to 95/5, with a flow rate of 0.5 ml/min and UV (224 nm) detection.[22]

Computational

Ab initio gas phase calculations were conducted using GAUSSIAN 09.[23] All structures were optimized at the MP2 [24–28] level of theory using the 6-311++G** basis set.[29–32] The complexes were verified as minima on the potential energy surface through vibrational analysis. Association energies were calculated considering unscaled zero point vibrational energies and thermal corrections. The solvation calculations were obtained with the CPCM [33,34] model included in the GAUSSIAN 09 package, with simulated dichloromethane as solvent. The results were visualized using CYLView.[35]

RESULTS AND DISCUSSION

Kinetic studies

Given the availability of classical hydrogen bond acceptors via both intramolecular (ketone carbonyl oxygen) and intermolecular (alcohol-OH sites) interactions, it was important to assess the occurrence of dihydrogen bonding and its behavior in the

reacting combination of hydroxyketone and tetrabutylammonium borohydride. The classical *versus* dihydrogen bonding distinction is easily detected via infrared spectroscopy as seen in Fig. 3. In this case, the OH peak, which was observed at 3450 cm^{-1} in a solution of 2-hydroxycyclopentanone in 1,2 DCB, shifted to 3250 cm^{-1} when tetrabutylammonium borohydride was added. This band, indicative of a dihydrogen bonding interaction, remained unchanged during the reaction. Importantly, there was no gas bubbling, suggesting that little or no H_2 formation took place between the OH and borohydride. Likewise, no loss in OH bond intensity was seen over the course of the reaction (see Fig. 4). An important reference for these observations is the interaction of cyclopentanol itself with tetrabutylammonium borohydride. There the OH bond shifts from 3609 to 3412 cm^{-1} upon addition of NBu_4BH_4 to a solution of alcohol in dichloromethane.

The reaction kinetics were found to be first order in ketone (see Fig. 5). Although the present studies supply NBu_4BH_4 in excess, studies from other groups with closely related borohydride compounds have likewise reported reduction kinetics to be first order in BH_4^-.[5] Application of the ketone and borohydride concentrations in the rate equations led to integrated rate laws and the corresponding rate constants, Table 1, and activation parameters, Table 2.

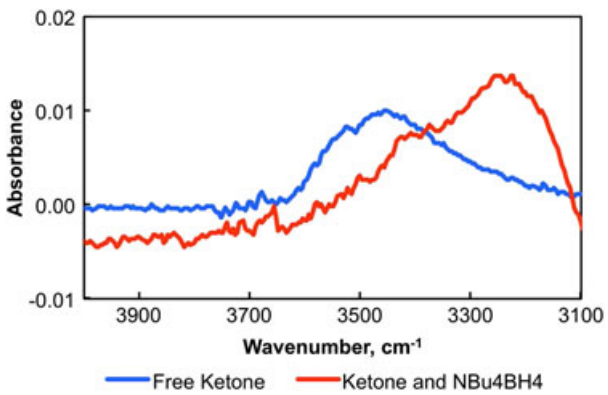


Figure 3. Hydroxyl shift of 2-hydroxycyclopentanone in presence of $NBu_4BH_4^-$

For comparison with 2-hydroxycyclopentanone, the reductions of cyclopentanone by NBu_4BH_4 in 1,2-DCB and in 2-propanol were also performed and the activation parameters determined, Table 2. The new activation parameters for cyclopentanone reduction in 2-propanol fall within the range of values determined earlier for cyclic ketones in the same solvent but with a different borohydride reducing agent, $NaBH_4$:

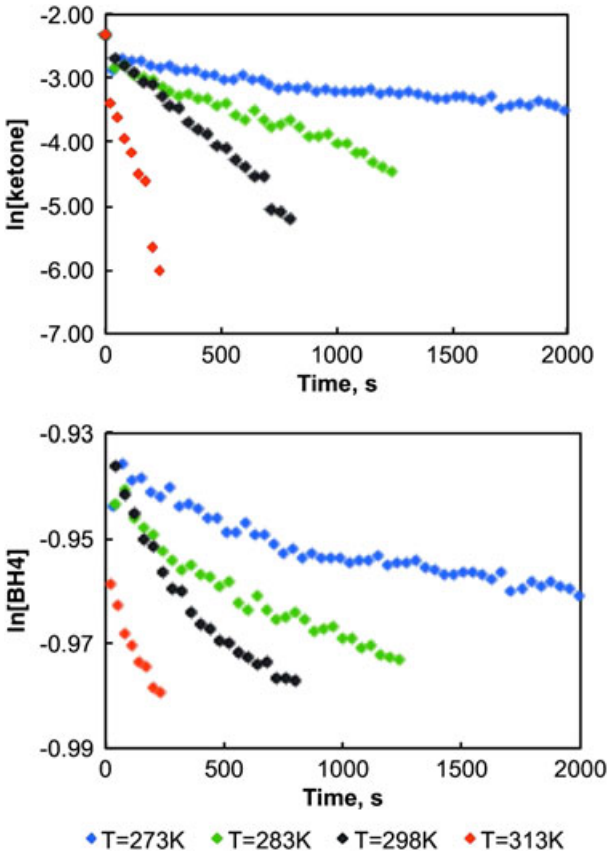


Figure 5. Time evolution of reagent concentrations

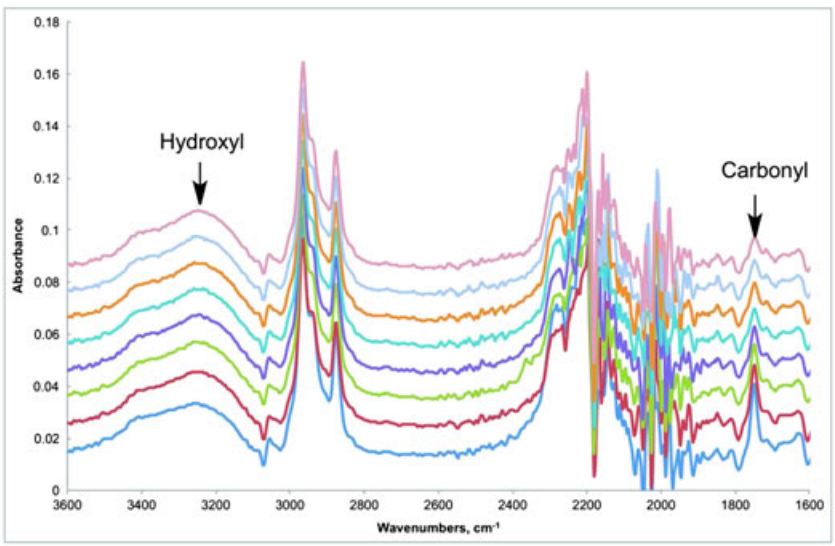


Figure 4. IR spectra of reduction of 2-hydroxycyclopentanone by $NBu_4BH_4^-$ in 1,2-dichlorobenzene at room temperature

Table 1. Rate constants for the reduction of 2-hydroxycyclopentanone by NBu_4BH_4

Temperature, K	k, $[l \cdot mol^{-1} \cdot s^{-1}] \cdot 10^3$
274	0.33 ± 0.027
283	1.00 ± 0.033
298	2.20 ± 0.160
315	8.10 ± 0.890

a solvent: 1,2-diclorobenzene; [ketone] = 0.1M; $[NBu_4BH_4]$ = 0.4M

5.4–11.1 kcal/mol and −36.4 to −48.4 e.u. for activation enthalpy and entropy, respectively.[5] Replacement of 2-propanol with 1, 2-DCB, a non hydrogen-bonding solvent, eliminates the opportunity for either dihydrogen or classical hydrogen bonding. In that regard, reduction of cyclopentanone in 1,2-DCB should be considered the reference system. Indeed, this solvent switch raises the activation enthalpy by 9 kcal/mol, suggesting that there is no activation of either the carbonyl or the borohydride.

The overall negative value of the activation entropy suggests a reduction of the degrees of freedom at the transition state as might be expected with a cyclic structure. In the case of 2-propanol, solvent molecules may be locked down due to charge development at the transition state. By contrast, the more weakly interacting solvent, 1,2-DCB, is less affected, thus, the reduction's activation entropy is more positive by 21.4 e.u. in 1,2-DCB than in 2-propanol.

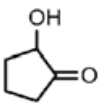
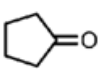
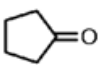
When 2-hydroxycyclopentanone is used as a substrate, BH_4^- is able to interact with the hydroxyl group via dihydrogen bonding, and its activation leads to a lower reaction barrier. With respect to activation entropy, we found a value that is close to the cyclopentanone/1,2-DCB system since the charge development at the transition state has an effect only on the hydroxyl moiety that is already constrained as a functional group of the substrate.

Stereochemical studies

From both mechanistic and synthetic points of view, it is of interest to understand the influence of different factors on stereochemical outcome. When we used the same work-up procedure employed earlier by Gatling and Jackson, followed by gas chromatography analysis, we reproduced the findings previously obtained for reduction of 2-hydroxycyclopentanone in dichloromethane. Direct analysis via HPLC, however, showed a much smaller directing effect (see Table 3 entry 6) *trans:cis* ratio of 63:37 as opposed to the 99.7:0.3 reported earlier.[36] When the reaction was conducted at high dilution and low temperature, the selectivity for the *trans* diol increased, as shown in entries 4 and 8 in Table 3, but it never approached the magnitude of the previous report.

Several reasons may account for the lack of stereocontrol: (i) flexibility of the cyclopentane ring which would weaken the preference for attack of BH_4^- from the face syn to the –OH group, (ii) the ability to form an internal hydrogen bond to the carbonyl oxygen resulting in competition with the dihydrogen bond, and (iii) possible lack of face selectivity for the later-formed (but presumably more reactive) alkoxyborohydride species. The first hypothesis was tested by using a more rigid substrate, 2-hydroxyacenaphthylen-1(2H)-one, Scheme 2, in which the conformation is locked by the naphthalene backbone moiety. Analysis of the reaction mixture resulting from reduction of 2-hydroxyacenaphthylen-1(2H)-one by NBu_4BH_4 in CH_2Cl_2 reveals that while the *trans* diol is the major product, *cis* diol is also formed in a ratio, *trans:cis* = 66:34, very similar to that seen in the 2-hydroxycyclopentanone case. Hence, while there is flexibility in the five-membered ring, it has little if any effect on the product distribution. The second hypothesis can be eliminated on the basis of both experimental and theoretical results. As mentioned earlier, addition of borohydride to the reaction mixture leads to a red shift of the hydroxyl frequency indicative of a dihydrogen bonding interaction. Ab initio gas-phase studies of 2-hydroxycyclopentanone interacting with NMe_4BH_4 provide insight in this regard. We were surprised to find an internal hydrogen bond in the energy minimized structure of isolated 2-hydroxycyclopentanone, with a close contact O. . .H of 2.30 Å, characteristic of a full fledged hydrogen bond. However, when $NMe_4BH_4^-$ is included in the calculations, a complex with a bifurcated pair of dihydrogen bonds is found to be more stable by 4.06 kcal/mol than the corresponding complex that has only the internal hydrogen bond (Fig. 6) suggestive of a stronger stabilizing effect via dihydrogen bonding. The solvation of the two complexes reduces the energetic gap to 1.50 kcal/mol but does

Table 2. Activation parameters for ketone reductions

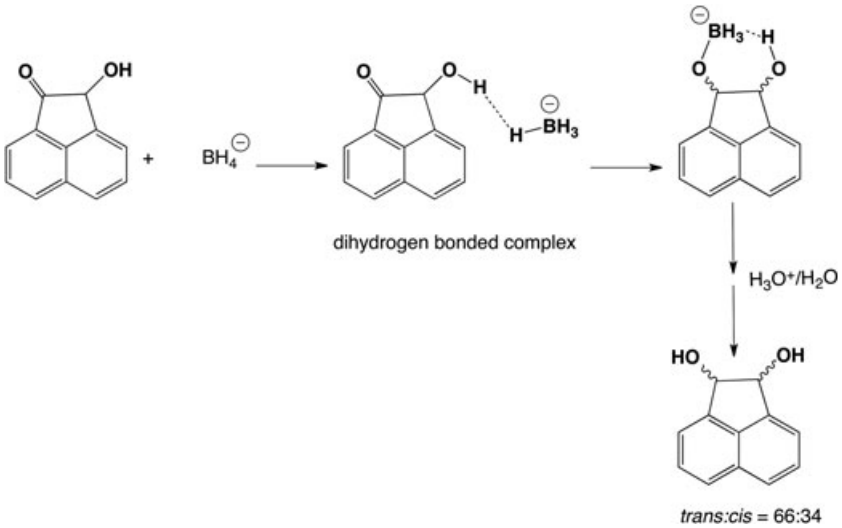
Substrate	Solvent	$\Delta H^{\neq}$, [kcal/mol]	$\Delta S^{\neq}$, [e.u.]	k[b], $[l \cdot mol^{-1} \cdot s^{-1}]$
	1, 2-DCB[a]	12.2 ± 1.13	-29.6 ± 3.88	2.20×10^{-3}
	1,2-DCB	18.8 ± 0.23	-22.9 ± 0.67	1.00×10^{-7}
	2-Propanol	9.8 ± 1.07	-44.3 ± 3.31	8.82×10^{-5}

[a]. 1,2-DCB = 1,2-dichlorobenzene;
[b]. rate constants at room temperature; note that the rate constant for reduction of cyclopentanone in 1,2-DCB is extrapolated from the activation parameters at higher temperatures.

Table 3. Trans:cis ratios in 2-hydroxycyclopentanone reduction

Entry	[ketone][a]	[NBu_4BH_4]	[ketone]/[NBu_4BH_4][b]	trans diol, %	cis diol, %
1	8.21×10^{-3}	5.31×10^{-1}	1:40	62.0	38.0
2	1.06×10^{-1}	3.68×10^{-1}	1:4	68.4	31.6
3	4.65×10^{-3}	4.97×10^{-3}	1:1	69.2	30.8
4	1.11×10^{-2}	1.23×10^{-2}	1:1	65.6	34.4
5 [c]	1.31×10^{-2}	1.63×10^{-2}	1:1	71.7	28.3
6	3.21×10^{-1}	3.58×10^{-1}	1:1	62.8	37.2
7 [c]	4.28×10^{-3}	1.49×10^{-3}	3:1	79.6	20.4
8	7.76×10^{-2}	1.63×10^{-2}	5:1	72.6	27.4
9	7.35×10^{-2}	8.19×10^{-3}	10:1	76.8	23.2

[a]. ketone: 2-hydroxycyclopentanone; solvent: CH_2Cl_2; temperature: 25 °C;
[b]. rough ratio values; c. temperature: 0 °C



Scheme 2. Reduction of 2-hydroxyacenaphthylen- 1(2H)-one by BH_4^-

not change the trend. These findings are in line with the IR observation of hydroxyl shifting upon NBu_4BH_4 addition, Fig. 3.

It has been reported that all four hydrides are available for reduction, and no disproportionation products have been detected. It is generally accepted [5,6,10] that in carbonyl reductions by BH_4^- ions, transfer of the first hydride is the RDS, but the products are formed via transfer of all hydrides. Thus, if the first hydride were selectively transferred from the dihydrogen bonded face of the ketone, it would lead to the *trans* diol but would account for only 25% of the product, while the rest of the stereochemical distribution would be dictated by the selectivities of the other three hydrides. Ab initio modeling of $CH_3OH...BH_x(OCH3)_{4-x}$, (x = 1, 2, 3, 4) complexes at the MP2/6-311++G** level showed that the OH functionality prefers the O from methoxy groups attached to boron to the hydride if it is available, i.e. hydrogen bonding is favored over dihydrogen bonding, presumably due to charge build up at the electronegative oxygen (the association energies are provided

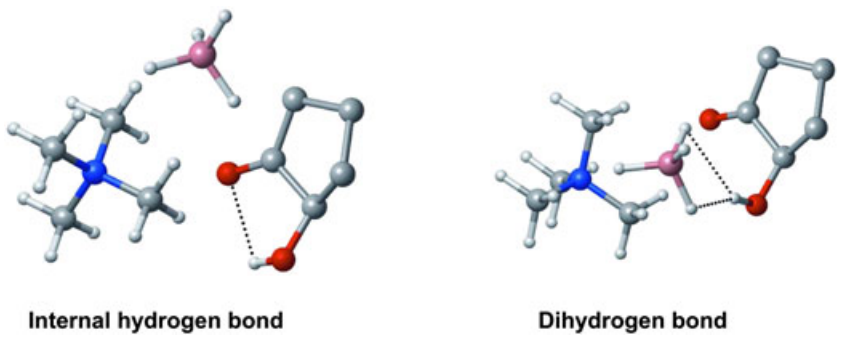


Figure 6. Complexes of 2-hydroxycylopentanone and NMe_4BH_4

in supporting information). This theoretical result suggests that the intermediates are hydrogen bonded to the carbonyl substrate. Looking at Table 3, concentration combinations with the greatest selectivity are those where [BH_4^-] is lowest, suggesting that if anything, the alkoxyborohydride species would be more selective than BH_4^-. Additional computational work is underway to elucidate the geometry of transition states and potential roles of alkoxyborohydride species in the overall mechanism of the reaction.

CONCLUSIONS

We have shown that dihydrogen bonding activates 2-hydroxyketones for reduction with NBu_4BH_4 by lowering the activation enthalpy by 6.6 kcal/mol. While the activation entropy is a significant component of the barrier, the changes resulting from the occurrence of dihydrogen bonding are manifested predominantly in the enthalpy term. Computational studies and infrared spectra confirm that while the carbon backbone allows for internal hydrogen bonding, that interaction is outweighed by dihydrogen bonding once BH_4^- is present in the system. The lack of stereocontrol is not due to the flexibility of the substrate backbone or to the selectivity among hydride or alkoxide sites in $HBH_n(OR)_{3-n}^-$. Future work will include modeling of the transition state geometry and energetics.

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[36] The procedure employed by Gatling and Jackson involved hydrolysis via treatment with H_2O_2 followed by NaOH and subsequent derivatization of the diol products to obtain the corresponding silyl derivatives that were analyzed by gas chromatography. While our own experiments reproduced the trans:cis ratio, the carbon balance was low due to the high stability of the alkoxyborate species corresponding to the cis diol. However for our studies, hydrolysis was achieved via treatment with H_2SO_4. The exothermicity of the reaction led to complete removal of the reaction solvent, dichloromethane, thus ensuring that all species were in an aqueous solution that was analyzed subsequently by HPLC. Removal of borate salts was achieved by treatment with a methanolic solution of HCl. The carbon balance for the latter method showed that all products were hydrolyzed and there was no starting ketone present.