Reactivity Control via Dihydrogen Bonding: Diastereoselection in Borohydride Reductions of α-Hydroxyketones

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Several reports of hydrogen bonding between hydridic and protonic hydrogen centers ("dihydrogen bonding") have explored the structural and electronic characteristics of these interactions,[1a,b] demonstrated their significance in both intra- and intermolecular examples,[1a,b,d] and developed estimates of the associated energetics.[1c,e,f] Of particular interest is the work concerning borohydrides; the water stability of these salts has been known for six decades, and they are among the most common and versatile reducing agents in the organic chemist's toolbox.

In 1994, we structurally examined $NaBH_4 \cdot 2H_2O$, uncovering three close BH···HO contacts (neutron diffraction distances 1.79, 1.86, and 1.94 Å in $NaBD_4 \cdot 2D_2O$). Ab initio calculations and liquid-phase IR studies[2c] confirmed that these polar H···H interactions are best understood as true hydrogen bonds with substantial charge transfer and interpenetration of the van der Waals surfaces.[2a,b] *They should also influence reactivity.* Indeed, dihydrogen bonding in crystals can direct solid-state topochemical loss of H_2 to yield covalent products different from those obtained in fluid phases.[3] This report demonstrates control by dihydrogen bonding of a typical solution borohydride reaction—ketone reduction—as depicted in Scheme 1.

The reaction substrates, 2-hydroxycycloalkanones **1**, **3a**, and **5**, were selected with the guidance of AM1 calculations and simple structural models. In the constrained frameworks of **1** and **3**, intramolecular hydrogen bonding between −OH and carbonyl moieties is geometrically impossible and thus could not induce directing or rate effects. The relative rigidity of these cyclic ketones also avoids conformational complexity. Chlorinated solvents and the borohydride's tetrabutylammonium countercation were chosen to be incapable of hydrogen bonding to either borohydride or substrate.

Figure 1 displays transition-state (TS) structures for BH_4^- reduction of 2-hydroxycyclobutanone (**1**), calculated using the semiempirical AM1 molecular orbital method.[4] The (hydrogen bonded) TS for attack on the −OH face is lower by 3.5 kcal/mol than that for the unsubstituted face. Both TSs lie substantially below the sum of the separate reactants' energies, as expected for a theoretical model that simulates gas-phase species.[5]

Table 1 summarizes experimental results for substrates **1**−**9**.[6] A key finding is that reduction of **1** and **3a** by tetrabutylammonium borohydride in chlorinated solvents gave almost exclusively the trans diol products.[7] This facial selectivity agrees well with the AM1 results, despite the crude level of theory and the absence of any solvent or counterion effects in the model. Strikingly, compounds **1** and **3a** also reacted >100 times faster than the

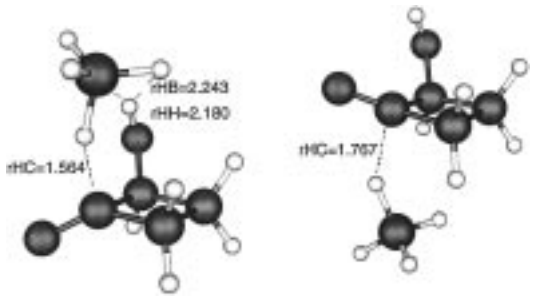
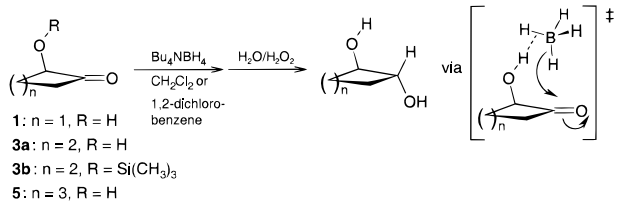


Figure 1. AM1-calculated transition structures for attack of BH_4^- from (left) syn ($\Delta H_f = -81.8$ kcal/mol) and (right) anti ($\Delta H_f = -78.3$ kcal/mol) faces of 2-hydroxycyclobutanone **1**.

Scheme 1



1: n = 1, R = H
3a: n = 2, R = H
3b: n = 2, R = $Si(CH_3)_3$
5: n = 3, R = H

Table 1. Summary of Hydrogen Bond-Directed Ketone Reduction Experiments[a]

substrate	solvent	additive	additive concn (M)	$t_{1/2}$[c]	cis diol	trans
1	DCB[b]			<1 min	<0.1	>99.9
2	DCB			2 h		
3a	DCB			7 min	1.4	96.6
3a	CH_2Cl_2			8 min	0.3	99.7
3a	CH_2Cl_2	CH_3OH	15.5	<1 min	4.4	95.6
3a	CH_2Cl_2	*tert*-amyl[b]	0.9	30 min	8.0	92.0
3a	CH_2Cl_2	TBAF[b]	0.25	120 min	54.5	45.5
3a	CH_2Cl_2	TBACl[b]	0.25	57 min	20.3	79.7
3a	CH_2Cl_2	TBABr[b]	0.25	20 min	6.5	93.5
3b	CH_2Cl_2			6 h	39.0	61.0
4	CH_2Cl_2			17 h		
4	CH_2Cl_2	TBABr[b]	0.35	13 h		
4	CH_3OH			20 min		
5	CH_2Cl_2			4 min	48.5	51.5
6	CH_2Cl_2			22 h		
7	CH_2Cl_2			21 h		
8	CH_2Cl_2			24 h		
9	CH_2Cl_2			35 h		

[a] Reactions were run at 25 °C with substrate and tetrabutylammonium borohydride initial concentrations of 0.25 M. As with most borohydride ketone reductions, yields were typically 90−100% with no side products observed. [b] Abbreviations: DCB = 1,2-dichlorobenzene; *tert*-amyl = *tert*-amyl alcohol; TBAF = tetrabutylammonium fluoride; TBACl = tetrabutylammonium chloride; TBABr = tetrabutylammonium bromide. [c] Values of $t_{1/2}$ were determined by IR monitoring of reaction progress. Uncertainties are typically ±10%.

(1) (a) Lee, J. C.; Peris, E.; Rheingold, A. L.; Crabtree, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 11014. (b) Crabtree, R. H.; Siegbahn, P. E. M.; Eisenstein, O.; Rheingold, A. L.; Koetzle, T. F. *Acc. Chem. Res.* **1996**, *29*, 348. (c) Qiang, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1995**, *117*, 10108. (d) Park, S.; Lough, A. J.; Morris, R. H. *Inorg. Chem.* **1996**, *35*, 3001. (e) Alkota, I.; Elguero, J.; Concepcion, F.-F. *J. Chem. Soc., Chem. Commun.* **1996**, 1633. (f) Gelabert, R.; Moreno, M.; Lluch, J. M.; Lledos, A. *Organometallics* **1997**, *16*, 3805.

(2) (a) X-ray and neutron diffraction studies of $NaBH_4 \cdot 2H_2O$ and $NaBD_4 \cdot 2H_2O$: Huang, R.; Sharma, M.; Eckert, J.; Argyriou, D.; Sheldon, R.; Jackson, J. E. Manuscript in preparation. (b) Sharma, M. Report to the Westinghouse Science Talent Search Committee, Fall 1994. (c) Wilson, C.; Inman K.; Jackson, J. E. Manuscript in preparation.

(3) (a) Custelcean, R.; Jackson, J. E. *J. Am. Chem. Soc.* **1998**, *120*, 12935. (b) Custelcean, R.; Jackson, J. E. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1661.

(4) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(5) AM1 energies (kcal/mol): BH_4^-, −2.9; **1**, −68.0; vdW complex syn to −OH, −86.3; vdW complex anti to −OH, −81.5; TS syn to −OH, −81.8; TS anti to −OH, −78.3.

(6) Substrates **2**, **4**, and **6**−**9** were purchased from Aldrich Chemical Co. and used without further purification. Compounds **1** and **3** were prepared via acyloin reactions of dimethyl succinate and dimethyl glutarate, respectively, following the literature procedure for preparation of **1** (see: Johnson, C. R. *Organic Syntheses*; Johnson, C. R., Ed.; John Wiley & Sons: New York, 1977; Vol. 57, pp 1−7). Compound **5** was obtained by treating its dimer (adipoin purchased from Aldrich) with dilute (5%) HCl. The product was extracted with dichloromethane, dried, and stripped of solvent.

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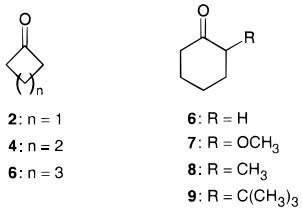
corresponding simple cycloalkanones **2** and **4**. This rate increase is too large to be attributed to an inductive effect, though it is known that α-substitution by an electron-withdrawing group can accelerate ketone reduction.[8] Thus, the silylated analogue **3b** is reduced only 3 times as fast as is simple cyclopentanone (**4**), and with very little stereochemical preference. Similarly, reduction rates of substituted cyclohexanones **6**−**9** under the current reaction conditions are not very sensitive to α-substituents.



2: n = 1
4: n = 2
6: n = 3

6: R = H
7: R = OCH_3
8: R = CH_3
9: R = $C(CH_3)_3$

Both the stereochemical outcome and the rate acceleration due to the α-hydroxy group in **1** and **3a** are consistent with a large enhancement (a factor of >100) in the rate of attack by borohydride on the carbonyl face syn to the −OH group. As predicted, the OH···BH_4^- dihydrogen bonding interaction guides the hydride delivery to produce (after hydrolysis) the trans diol product. If the rate of attack on the non-hydroxylated face is estimated to be the same as that for reaction at one of the two faces of the simple cycloalkanone, the rate enhancement should be about one-half the factor by which the −OH face is preferred.

It is important to rule out a process in which an initial bond-forming reaction of BH_4^- with the −OH site is followed by intramolecular hydride delivery, as is the case with the triacetoxyborohydride reductions reported by Saksena[9a] and Evans[9b] and recently reviewed by Gribble.[9c] Fortunately, FTIR easily shows that the OH···BH_4^- dihydrogen bonding occurs prior to reduction, and neither H_2 evolution nor depletion of the −OH absorption band is observed during the reaction. Likewise, the −OH groups of cyclobutanol and cyclopentanol do not react with BH_4^- over 32 h, substantially longer than the ketone reductions require.

The above picture predicts a loss of rate and stereodirecting effects when an added hydrogen bonding reagent, such as an alcohol, interacts with the BH_4^-, −OH, and C═O fragments. In fact, the trans:cis diol ratio for reduction of **3a** decreased from >300:1 to 22:1 when methanol was added, but the rate also increased at least 8-fold (see Table 1). Unlike the less acidic higher alcohols, methanol does react to lose H_2 with formation of $(CH_3O)_nBH_{4-n}^-$ species, which are known[10] to be more powerful hydride donors than BH_4^-. Hydroxylic solvents are also thought to accelerate reductions of simple ketones by hydrogen bonding to the carbonyl group, stabilizing the developing negative charge during hydride delivery.[11] Thus, even for cyclopentanone **4**, switching to methanol solvent accelerates reduction ca. 50-fold. The bulky *tert*-amyl alcohol, which hydrogen bonds but does not react with borohydride, causes the expected decrease in rate and in facial preference. Tetrabutylammonium fluoride (TBAF), chloride (TBACl), and bromide (TBABr) also inhibit the reaction, presumably by competing with borohydride for hydrogen bonding to the substrate's hydroxyl group. The stronger the hydrogen bonding nature of the halide (TBAF > TBACl> TBABr), the greater the effect on the reduction rate ($t_{1/2}$ = 120, 57, and 20 min, respectively, for 1:1 halide:borohydride mixtures) and stereoselectivity (trans:cis ratios of 0.8:1, 3.9:1, and 14.4:1, respectively).[12] For reference, TBABr has almost no effect on the reduction of cyclopentanone **4**. Trimethylsilyl ether **3b** provides confirmation that the −OH group is key to the rate enhancement and stereocontrol. With the OH···BH_4^- interaction blocked, the reaction half-life increases from 8 min for **3a** to 6 h for **3b**.

In 2-hydroxycyclohexanone **5**, the presence of the −OH group induced a 300-fold rate increase over simple cyclohexanone **6** but essentially no stereoselectivity (∼1:1 cis:trans diol). In chair **5**, the equatorial −OH may activate the coplanar carbonyl group through intramolecular hydrogen bonding, or it may hydrogen bond to BH_4^- ; both possibilities should accelerate reaction without a significant facial preference. The seemingly anomalous behavior of **5** thus supports the notion that, in the flatter frameworks **1** and **3**, with the −OH group firmly on one side of the C═O plane, stereocontrol and rate enhancement arise via OH···BH_4^- dihydrogen bonding.

We believe the above results represent the first recognized instance of a directing effect specifically mediated by dihydrogen bonding. Such interactions must have influenced numerous previous studies, but their contributions have gone undetected in the context of a given substrate or have been muddied by the presence of hydrogen bonding solvents, Lewis acidic counterions and additives, or other stereochemical biases. The strength of the facial preference, however, promises useful stereo- and regiocontrol of reactions involving hydride reagents.

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(7) In a typical experiment, 0.64 g (2.5 mmol) of solid tetrabutylammonium borohydride was added to a solution of ketone (2.5 mmol) in dichloromethane (10 mL), and the reaction vessel was vigorously shaken or stirred and then allowed to stand for 0.25−150 h with periodic monitoring by IR and/or NMR. Quenching with 20 mL of 3% hydrogen peroxide, followed by 10 mL of 10% sodium hydroxide, was followed by layer separation and extraction of the aqueous phase with three 30-mL portions of dichloromethane. The combined organic solutions were extracted with 20 mL of saturated sodium sulfite, dried over anhydrous sodium sulfate, and concentrated under reduced pressure (note, the diol products are very water soluble and therefore difficult to extract into the organic phase). The crude product was taken up in anhydrous diethyl ether, the insoluble tetrabutylammonium salts were removed by filtration, and the ether solvent was evaporated. Quantitative analysis was carried out by conventional trimethylsilylation/capillary gas chromatography.

(8) The reactivity of α-substituted benzyl phenyl ketones with $NaBH_4^-$ in propan-2-ol increases in the order of H < OH < OMe with reduction rate constants of 2.69×10^3, 98.6×10^3, and 238.6×10^3 L mol^{-1} s^{-1}, respectively. Presumably, the electron-withdrawing nature of the substituent facilitates the nucleophilic attack of BH_4^- on the carbonyl carbon. See: Krishnan, K.; Chandrasekaran, J. *Indian J. Chem.* **1982**, *21B*, 595.

(9) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. (c) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395.

(10) (a) Wuesthoff, M. T. *Tetrahedron* **1973**, *29*, 791. (b) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (c) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.

(11) (a) Wigfield, D. C.; Gowland, F. W. *J. Org. Chem.* **1977**, *42*, 1108. (b) Pierre, J.-L.; Handel, H. *Tetrahedron Lett.* **1974**, 2317.

(12) The fluoride result, in which the stereopreference is actually reversed, suggests that it might be possible to use this strategy to intentionally disfavor hydroxylated sites.