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Requirements for Selective Hydrophobic Acceleration in the Reduction of Ketones

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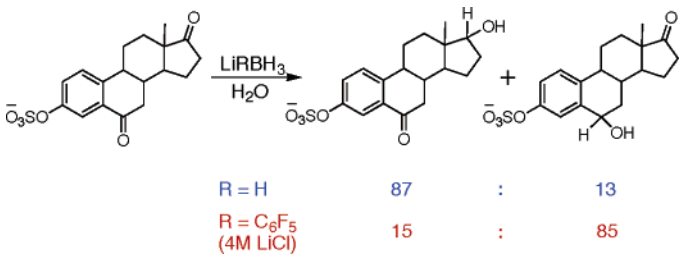
ABSTRACT



Reductions of various quaternized hydrophobic β-keto amines were performed in water and in methanol using borohydride anions carrying hydrophobic groups. The most important requirement of the substrate to permit hydrophobically accelerated selective reductions is the ability of the hydrophobic group of the substrate and its attached keto group to attain a coplanar relationship. Some derivatives of naturally occurring steroid diones have also been employed as substrates to probe the mechanism and utility of these hydrophobically accelerated selective reductions further.

The hydrophobic effect is the tendency of nonpolar surfaces to aggregate in water in order to lower the free energy by minimizing their interfacial hydrocarbon−water contacts.[1] In our laboratory, the hydrophobic effect has been implicated in the dramatic rate enhancements that are observed when Diels−Alder reactions[2] and benzoin condensations[3] are performed in an aqueous medium. In each of these coupling reactions, we have proposed that hydrocarbon packing intrinsic to the transition states results in a lower energy of activation and thereby a rate acceleration. Building on these observations, we have also developed a method to analyze the geometry of transition states by determining the extent that phenyl rings and other hydrophobic units pack in the transition state.[4]

Recently, we reported that the hydrophobic effect could also be exploited to accelerate atom-transfer reactions.[5] We showed that in competition reactions enhanced reactivity can be achieved for substrates bearing a hydrophobic group when the reaction medium is changed from organic to aqueous and a hydrophobic reagent is employed. Specifically, we demonstrated that $LiC_6F_5BH_3$ accelerates the selective reduction of a naphthyl ketone over a methyl ketone in water 40-fold when compared with the same reaction using $LiBH_4$ in methanol. In that study, a general trend was established in which increased hydrophobicity was directly related to increased reactivity for reductions conducted in water.

To understand more completely the requirements and mechanism of these hydrophobically accelerated reductions, it is important to compare the relative rates of reduction achieved when ketones and borohydrides with substituents of different hydrophobicity and steric demand are employed. Herein, we assess the propensity of a range of hydrophobic groups to accelerate the reduction of ketones when the

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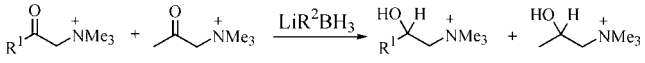
Table 1. Ratios of Products **3**/**4** Formed in the Competition Reactions of Quaternized β-Keto Amines **1** and **2** with Substituted Borohydrides under Different Reaction Conditions[a–d]



1a: R^1 = Phenyl **2** **3** : **4**
1b: R^1 = 2-Naphthyl
1c: R^1 = 1-Naphthyl
1d: R^1 = Cyclohexyl
1e: R^1 = Benzyl

	R^2	D_2O	4 M LiCl/D_2O	CD_3OD
1a	H	44:56 (0.143)	47:53 (0.071)	31:69 (0.474)
1a	Ph	56:44 (−0.143)	64:36 (−0.341)	35:65 (0.367)
1a	C_6F_5	74:26 (−0.620)	84:16 (−0.983)	40:60 (0.240)
1b	H	53:47 (−0.071)	52:48 (−0.047)	35:65 (0.367)
1b	Ph	67:33 (−0.420)	72:28 (−0.560)	38:62 (0.290)
1b	C_6F_5	91:9 (−1.371)	95:5(−1.745)	54:46 (−0.095)
1c	H	32:68 (0.447)	32:68 (0.447)	19:81 (0.859)
1c	Ph	40:60 (0.240)	42:58 (0.191)	30:70 (0.502)
1c	C_6F_5	60:40 (−0.240)	64:36 (−0.341)	23:77 (0.716)
1d	H	29:71 (0.531)	30:70 (0.502)	31:69 (0.474)
1d	Ph	32:68 (0.447)	32:68 (0.447)	32:68 (0.447)
1d	C_6F_5	20:80 (0.821)	20:80 (0.821)	16:84 (0.982)
1e	H	59:41 (−0.216)	56:44 (−0.143)	60:40 (−0.240)
1e	Ph	56:44 (−0.143)	53:47 (−0.071)	54:46 (−0.095)
1e	C_6F_5	54:46 (−0.095)	54:46 (−0.095)	53:47 (−0.071)
1f	H	57:43 (−0.167)	54:46 (−0.095)	50:50 (0.000)
1f	Ph	47:53 (0.071)	49:51 (0.024)	50:50 (0.000)
1f	C_6F_5	50:50 (0.000)	51:49 (−0.024)	55:45 (−0.119)
1g	H	7:93 (1.533)	7:93 (1.533)	6:94 (1.630)
1g	Ph	27:73 (0.589)	31:69 (0.474)	18:82 (0.898)
1g	C_6F_5	41:59 (0.216)	47:53 (0.071)	14:86 (1.076)

[a] All reactions were carried to ca. 5% conversion. [b] Experiments with **1a**,**d**,**f**, **g** were conducted at a concentration of 20 mM. Experiments with **1b** were conducted at a concentration of 6 mM. Experiments with **1c** were conducted at a concentration of 10 mM. [c] Reported ratios are within an error of ±1% in at least duplicate runs. The top six entries of this table were previously published in ref 5. [d] $\Delta\Delta G^{\ddagger}$ (kcal/mol) for each reaction is in parentheses.

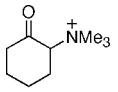
reaction medium is changed from organic to aqueous. By varying the hydrophobic part of the ketone and the borohydride, we have determined the requirements for rate acceleration in the hydrophobically directed reduction of ketones.

From competition reactions performed between methyl ketone **2** and aryl ketones **1a** and **1b** (Table 1), it is apparent that the increased hydrophobicity in changing from a phenyl **(1a)** to a 2-naphthyl group **(1b)** results in a significant rate enhancement for carbonyl reduction when the reactions are conducted in water using a hydrophobic reducing agent.[5] When the more hydrophobic[6,7] $LiC_6F_5BH_3$ is employed instead of $LiPhBH_3$ as the reducing agent, selectivity for the hydrophobic substrate likewise increases. (As we have discussed,[5] there may also be some assistance from quadrupolar forces when a perfluorophenyl group packs onto a normal aromatic ring.) The additional rate increases that result from the "salting-out" of the hydrophobic groups using lithium chloride—along with the rate decrease that results from a change to a methanolic medium—also strongly implicate the hydrophobic effect.[1a,3]

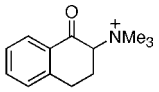
The hydrophobic acceleration of reduction that was observed using the 2-naphthyl derivative **1b** was not observed when the 1-naphthyl substrate **1c** was employed. Instead, the rate increase for **1c** in competition reactions with **2** was even smaller than that observed using the phenyl substrate **1a**. Because the rate increase is directly related to the amount of hydrocarbon packing permitted in the transition state, this result indicates that there is more hydrocarbon packing with **1b** than with **1c**. The smaller salt effect on the reduction of **1c** when compared with **1b** supports this interpretation.

Apparently the location of the carbonyl group of **1c** at the α-position on the naphthalene ring inhibits the formation of a conjugated planar relationship between the naphthalene ring and the carbonyl group, reflecting an unfavorable interaction that would result with the *peri* hydrogen of the naphthalene ring upon planarization. If the tendency of a hydrophobic group to be in a coplanar conjugated conformation decreases, the potential for removal of solvent-accessible nonpolar area through hydrophobic overlap in the transition state will decrease, while the steric demand that would be exerted by the substrate hydrophobic unit on the incoming borohydride will increase.

No hydrophobic acceleration of reduction was observed with the cyclohexyl substrate **1d** and the benzyl substrate **1e**. This lack of rate enhancement again reflects the inability of the hydrophobic group on the borohydride to pack efficiently on the cyclohexyl or benzyl group of the substrates in the transition state for hydride transfer. In each case, conformational flexibility of the hydrophobic group—allowing the carbonyl group to lie out of the plane of the phenyl or cyclohexyl group—will inhibit hydrophobic packing during hydride transfer. When $LiPhBH_3$ or $LiC_6F_5BH_3$ was used as the hydride source instead of $LiBH_4$, selectivity for substrate **1e** actually decreased. Apparently steric effects dominate the reduction of **1e**.



1f

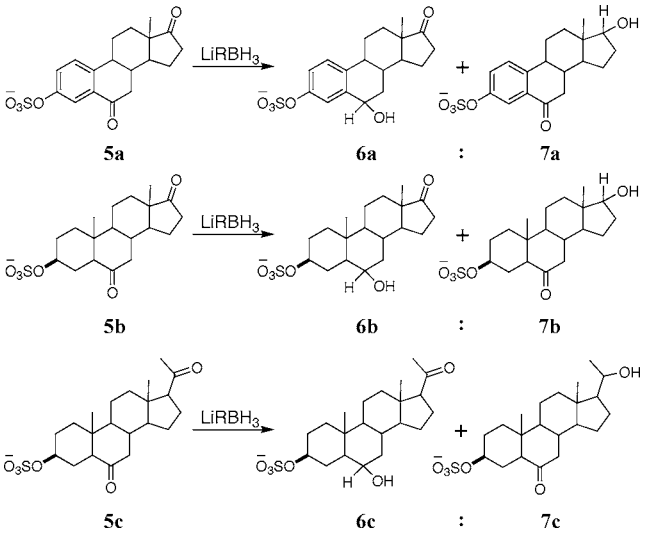


1g

To determine whether the propensity of an aryl ketone to assume a conjugated coplanar conformation is an important factor in the hydrophobic rate acceleration, we synthesized compound **1g** whose carbonyl group is held in coplanar conjugation. Because the cyclohexanone component of **1g** could also be considered a potential source of hydrophobic acceleration, compound **1f** was also examined. Competition reactions using **1f** (Table 1) show that the carbocyclic structure of cyclohexanone does not induce a hydrophobic acceleration of reduction. When experiments were performed using compound **1g**, the rate increase for reduction using

(6) Sheppard, W. A.; Sheetz, C. M. *Organic Fluorine Chemistry*; W. A. Benjamin, Inc.: New York, 1969.
(7) See the Supporting Information for a more efficient synthesis of $LiC_6F_5BH_3$ than previously reported in ref 5.

Table 2. Ratios of Products **6:7** Formed in the Partial Reduction of Steroid **5** under Different Reaction Conditions[a−c]



	R	D_2O	4 M $LiCl/D_2O$	1:1 CD_3OD/D_2O
5a	H	13:87 (1.126)	14:86 (1.076)	10:90 (1.302)
5a	Ph	60:40 (−0.240)	69:31 (−0.474)	32:68 (0.447)
5a	C_6F_5	78:22 (−0.750)	85:15 (−1.028)	46:54 (0.095)
5b	H	42:58 (0.191)	43:57 (0.167)	39:61 (0.265)
b	Ph	46:54 (0.095)	50:50 (0.000)	38:62 (0.290)
5b	C_6F_5	49:51 (0.024)	52:48 (−0.047)	39:61 (0.265)
5c	H	85:15 (−1.028)	84:16[d] (−0.982)	84:16 (−0.982)
5c	Ph	91:9 (−1.371)	93:7[d] (−1.533)	85:15 (−1.028)
5c	C_6F_5	94:6 (−1.630)	95:5[d] (−1.745)	83:17 (−0.939)

[a] All reactions carried to ca. 5% conversion and conducted at a concentration of 20 mM. [b] Reported ratios are within an error of ±1% in at least duplicate runs. [c] $\Delta\Delta G^{\ddagger}$ (kcal/mol) for each reaction is in parentheses. [d] Reaction performed in 2 M $LiCl/D_2O$.

$LiC_6F_5BH_3$ in D_2O was significantly larger than that observed in **1a**, in which the phenyl group is not fully frozen into coplanar conjugation. Since we have shown that the cyclohexanone component of **1g** cannot be responsible for the acceleration, the accessibility of hydrophobic binding during carbonyl attack, which results from the frozen coplanar conformation, must be responsible for this rate enhancement.

From these results we expected—and observed—a reversal of chemoselectivity in the reduction of the sulfated naturally occurring steroid **5a** (Table 2) when the $H_2O/LiC_6F_5BH_3$ combination was employed instead of either the $H_2O/LiBH_4$ or $CH_3OH/LiBH_4$ combinations.[8] When the reduction was performed using $H_2O/LiBH_4$ or $CH_3OH/LiBH_4$, reduction of the 6-keto group **(6a)** was disfavored compared to the reduction of the 17-keto group **(7a)** (13:87 and 10:90, respectively). However, when the reduction of **5a** was performed in 4 M $LiCl/D_2O$ with $LiC_6F_5BH_3$, a dramatic selectivity reversal was observed in which the reduction of the 6-keto group **(6a)** was strongly favored over the reduction of the 17-keto group **(7a)** in a ratio of 85:15.

The change in $\Delta\Delta G^{\ddagger}$ by simply changing from $LiBH_4/D_2O$ to the salted-out $LiC_6F_5BH_3$ is −2.154 kcal/mol, which corresponds to a 38-fold relative rate increase. This rate increase is comparable to that observed in the competition reactions of **1b** and **2** when the condition are changed from $LiBH_4$ in CD_3OD to $LiC_6F_5BH_3$ in 4 M $LiCl/D_2O$.

Such a large dependence of selectivity on the reaction medium and the borohydride substitutents was not seen when sulfated 6-ketoepiandrosterone **(5b)** was tested under identical conditions of hydrophobic reduction. The perfluorophenyl group on the borohydride is apparently not able to bind to the rigid decalin ring system of **5b** as well as it can bind to the flat and rigid tetralone ring system of **5a**. The similar hydrophobic environments of the 6-keto and 17-keto groups result in little change in selectivity when hydrophobic conditions are employed. Of course *both* keto groups in **5b** could be experiencing hydrophobic acceleration, but to a similar extent.

To determine if the rigid, saturated steroidal framework is capable of hydrophobically accelerating the reduction of a keto substituent, we synthesized the sulfate of 6-ketopregnenolone **(5c)** in which the rigid 17-keto group of **5b** is replaced with a more flexible acetyl group. In **5c**, the intrinsic reactivity of the 6-keto group is much greater than that of the 17-acetyl group, which is placed in a more sterically demanding environment. When the reduction is performed in CD_3OD/D_2O with $LiBH_4$, the 6-keto group is reduced preferentially over the 17-acetyl group in a ratio of 84:16. When $LiC_6F_5BH_3$ in 2 M $LiCl/D_2O$ is employed, the product ratio becomes 95:5, which corresponds approximately to a 4-fold relative rate increase over the non-hydrophobic conditions. This implies that the saturated steroidal framework does indeed provide some hydrophobic acceleration, although not as much as the unsaturated estrone framework does.

We investigated the effect of greater structural variation of the borohydride reagents on the observed rate increase in reductions conducted under hydrophobic conditions (Table 3). We synthesized three borohydride reagents: the known[9] sodium salt of a borohydride anion carrying both a cyano group and a benzyl group ($NaCNBnBH_2$), the novel lithium salt of a borohydride anion carrying two phenyl groups ($LiPh_2BH_2$), and our previously synthesized[5] lithium salt of a borohydride anion carrying a 2-naphthyl group ($LiNaphBH_3$).

The use of $NaCNBnBH_2$ in competitions of **2** with **1a** and **1b** indicates that a benzyl group has a very similar propensity toward hydrophobic reduction as does the phenyl group (Table 1). Thus, compared to the phenyl group of $LiPhBH_3$, the extra degree of rotational freedom in the benzyl group of $NaCNBnBH_2$ appears to have an almost negligible effect on its ability to bind to substrates **1a** and **1b**. The use of $LiPh_2BH_2$ shows that the availability of an additional phenyl group for hydrophobic packing is advantageous despite the additional intrinsic steric demand. It may contribute to reagent/substrate binding, or exert a useful steric effect.

(8) UV dilution experiments performed on substrates **1b** and **5a** indicate that appreciable aggregation of the substrates does not occur under the reaction conditions employed (see the Supporting Information).

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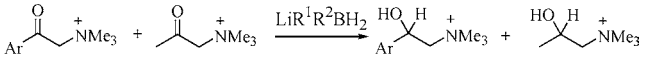
Table 3. Ratios of Products **3**/**4** Formed under Different Reaction Conditions in the Competition Reactions of Quaternized β-Keto Amines **1** and **2** with Borohydrides that Bear Varying Hydrophobic Units[a–d]



1a: Ar = Phenyl **2** **3** : **4**
1b: Ar = 2-Naphthyl

	R^1	R^2	D_2O	4 M LiCl/D_2O	CD_3OD
1a	Bn	CN	59:41 (−0.216)	64:36 (−0.341)	37:63 (0.315)
1b	Bn	CN	64:36 (−0.341)	67:33 (−0.420)	39:61 (0.265)
1a	Ph	Ph	65:35 (−0.367)	73:27 (−0.589)	39:61 (0.265)
1b	Ph	Ph	76:24 (−0.683)	81:19 (−0.859)	45:55 (0.119)
1a	$C_{10}H_7$	H	68:32 (−0.447)	74:26 (−0.620)	34:66 (0.393)
1b	$C_{10}H_7$	H	81:19 (−0.859)	85:15 (−1.028)	40:60 (0.240)

[a] All reactions carried to ca. 5% conversion. [b] Experiments with **1a** were conducted at a concentration of 20 mM. Experiments with **1b** were conducted at a concentration of 6 mM. [c] Reported ratios are within an error of ±1% in at least duplicate runs. [d] $\Delta\Delta G^{\ddagger}$ (kcal/mol) for each reaction is in parentheses.

Finally, upon changing from $LiPhBH_3$ to $LiC_{10}H_7BH_3$ in salted water, a change in $\Delta\Delta G^{\ddagger}$ of −0.468 kcal/mol is observed in the competition reaction of **1b** and **2**. Thus, the use of $LiC_{10}H_7BH_3$ again demonstrates that selectivity for the hydrophobic substrate in competition reactions varies directly with the amount of hydrophobic surface on the borohydride.

The most ideal situation for hydrophobic acceleration is one in which hydrophobic binding is intrinsic to the transition state of the reaction (e.g., endo Diels−Alder attack[2b]). By contrast, hydride transfer reactions can of course also occur in geometries in which hydrophobic packing is not involved. However, this study shows that by minimizing the steric burden of attack from the side of the aryl substituent, and by maximizing the hydrocarbon overlap when the attack does occur, significant hydrophobic contributions to selective rate accelerations in hydride transfer reactions can indeed be achieved. Studies to use such hydrophobic packing in stereoselective reductions are currently underway.

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Supporting Information Available: NMR, MS, and procedures for the synthesis of substituted borohydrides, quaternary salts **1a**−**e**,**g**, and steroids **5a**−**c**; UV spectra for dilution experiments with **1b** and **5a**; procedures for competition reactions and samples of ^1H NMR spectra from competition experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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