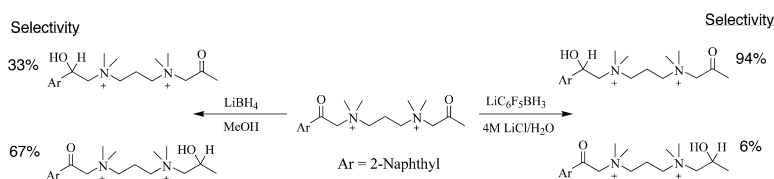


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Hydrophobically Directed Selective Reduction of Ketones

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The hydrophobic effect, the tendency of nonpolar surfaces to aggregate in water, is an intrinsic property of water that may be exploited to obtain reactivity unique to the aqueous medium.^{1,2} We have previously shown that the Diels–Alder reaction³ and the benzoin condensation⁴ are dramatically accelerated when conducted in water. The rate acceleration of these reactions results in part from the packing of hydrophobic surfaces in the transition state, which lowers the transition state energy by minimizing the interfacial hydrocarbon–water contact. Building on these observations, we have developed a method to detect the packing of phenyl rings and other hydrophobic units in the transition states of reactions in water solutions, reactions such as displacement reactions by anilines and phenoxide ions on benzylic halides.⁵ These are all coupling reactions of two reactants.

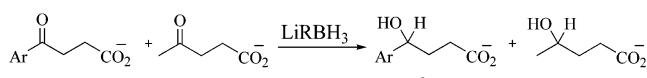
However, it seems likely that the phenomenon is general and that such atom-transfer reactions as hydride reductions and oxygenations would also be promoted and directed in water solution by the packing geometry that minimizes the water–hydrocarbon interface. Thus, we have now developed reducing agents that bear a discrete hydrophobic region, to effect the selective reduction of ketones that likewise have a hydrophobic environment. We wish to report the development of these hydrophobic reducing agents and the first examples of hydrophobically directed atom-transfer hydride reactions in water with substrate selectivity and regioselectivity.

We conducted the initial tests for hydrophobically directed reductions by performing aqueous competition reactions of levulinic acid (**1**) and 3-benzoylpropionic acid (**2a**) or 3- β -naphthoylpropionic acid (**2b**) with hydrophobic borohydride reducing agents (Table 1).⁶ We synthesized the hydrophobic borohydrides through the LiAlH₄ reduction of commercially available substituted boronic acids.⁷ We anticipated that the ratio of reduced levulinic acid to reduced substituted propionic acid in water would change when the reducing agent was changed from LiBH₄ to a more hydrophobic reducing agent, and indeed a change in reactivity was observed.

Reactions were performed in D₂O and carried to ca. 5% conversion, so as to measure the initial selectivities. Consistent with hydrophobic direction, the selectivity for the reduction of the hydrophobic substrate was greater with lithium β -naphthaleneborohydride than with the phenylborohydride. Likewise, the selectivity was greater when we employed 3- β -naphthoylpropionic acid in the competition reactions instead of 3-benzoylpropionic acid. In this system, the percent reduction of the hydrophobic substrate varies from a low of 37% when 3-benzoylpropionic acid is reduced by LiBH₄ in D₂O to a high of 68% when 3- β -naphthoylpropionic acid is reduced by novel LiNaphBH₃ in D₂O. Although only a modest selective rate increase was involved, these results suggested that hydrophobically directed atom-transfer was a source of the observed selectivity.

Additives such as salts or alcohols can be employed to either intensify or weaken hydrophobic effects.^{1,4,5} Salts such as LiCl and NaCl have been shown to increase hydrophobic interactions by

Table 1. Ratios of Products (**3:4**) Formed in the Competition Reactions of 3-Ketopropanoic Acids with Substituted Borohydrides under Different Reaction Conditions^{a,b}



2a : Ar = Phenyl
2b : Ar = Naphthyl

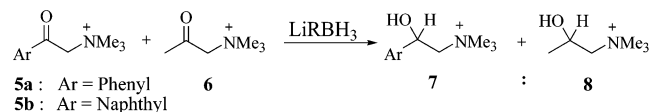
	R	D ₂ O	4:1 D ₂ O:CD ₃ OD	4 M NaCl/D ₂ O	4 M NaClO ₄ /D ₂ O
2a + 1	H	37:63	39:61	37:63	38:62
2a + 1	Ph	50:50	47:53	54:46	46:54
2a + 1	Naph	56:44	50:50	61:39	49:51
2b + 1 ^c	Naph	68:32	53:47	71:29	54:46

^a Reactions conducted with a substrate concentration between 100 and 200 mM. ^b All ratios are within an error of ± 1 in at least duplicate runs. ^c Substrate concentration of 4 mM.

electrostriction, “salting out” the hydrocarbon surfaces dissolved in water. When NaCl was added to the reaction medium, a modest increase in selectivity for the reduction of the hydrophobic substrate was observed (Table 1). Conversely, salts such as NaClO₄ and guanidinium chloride have been shown to decrease hydrophobic interactions by solvating the hydrocarbon surfaces dissolved in water.^{4,5} When NaClO₄ was added, we observed a decrease in selectivity for the reduction of the hydrophobic substrate. The addition of methanol to the reaction medium also (Table 1) decreased the selectivity for reduction of the hydrophobic substrate by hydrophobic reagents, but no effect was seen with LiBH₄. These salt and alcohol effects strongly implicate the hydrophobic effect as a driving force in the reductions where two hydrophobic surfaces are involved.

The potential for hydrophobically induced selectivity having been established, we created and studied a new group of ketones based upon quaternized β -keto amines (**5** + **6**) such that the selectivity obtained with ketones on separate molecules could be compared with the selectivity obtained when the hydrophobic and nonhydrophobic ketones were within the same molecule (**9a**, **9b**, and **9c**). In this group of ketones, we also tested lithium pentafluorophenyl borohydride (LiC₆F₅BH₃) as a reducing agent. We expected the perfluorinated reducing agent to be superior because of the elevated hydrophobicity that results from fluorination.⁸ Because of its electron deficiency, novel LiC₆F₅BH₃ would also be a weaker hydride donor than its nonfluorinated analogue and would possibly exhibit a favorable quadrupolar interaction with a nonfluorinated aryl group.^{9,10}

LiC₆F₅BH₃ did indeed prove to be the most selective reducing agent (Table 2). In competition reactions of **5b** and **6**, the naphthyl ketone was reduced preferentially over the methyl ketone in a 91:9 ratio. When salted out with LiCl, the selectivity increased to 95:5, whereas when LiBH₄ was employed, the product ratio was approximately 50:50. When the competition reactions of **5b** and **6** were performed in methanol using LiBH₄ and LiPhBH₃ separately, ratios of 36:64 and 38:62 were obtained, respectively. The ap-

Table 2. Ratios of Products (7:8) Formed in the Competition Reactions of Quaternized β -Keto Amines with Substituted Borohydrides under Different Reaction Conditions^{a,b}

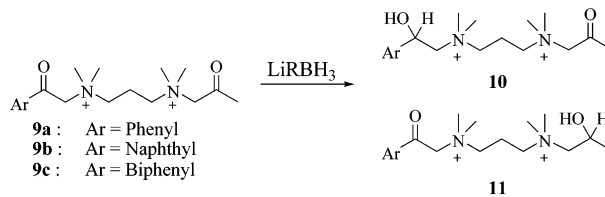
	R	D ₂ O	4 M LiCl/D ₂ O	CD ₃ OD
5a + 6	H	44:56	47:53	31:69
5a + 6	Ph	56:44	64:36	35:65
5a + 6	C ₆ F ₅	74:26	84:16	40:60
5b + 6	H	53:47	58:42	35:65
5b + 6	Ph	67:33	72:28	38:62
5b + 6	C ₆ F ₅	91:9	95:5	54:46

^a Experiments with **5a** were conducted at 20 mM and were carried to ca. 5% reduction of the ketones; experiments with **5b** were conducted at 6 mM. ^b All ratios are within an error of ± 1 in at least duplicate runs.

proximately equivalent ratio of reduction products obtained when nonhydrophobic and hydrophobic reducing agents were used reflects the absence of the hydrophobic effect in methanol. The (only slightly) elevated selectivity for the hydrophobic ketone when LiC₆F₅BH₃ was used as a reducing agent in methanol suggests that a quadrupolar interaction might make a small contribution to the selectivity with LiC₆F₅BH₃ in water.

As expected, the product ratios observed in the competition reactions with ketones on separate molecules are consistent with the ratios observed when the ketones are within the same molecule (Table 3). In addition to molecules with a phenyl or naphthyl group, intramolecular chemoselectivity experiments were also conducted in molecules containing a biphenyl group.¹¹ In all experiments, the naphthyl ketone was most selectively reduced using hydrophobic reducing agents, followed by the biphenyl ketone, and then the phenyl ketone.

Thus, we have shown that a reversal of 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. Novel LiC₆F₅BH₃ proved to be the most selective hydrophobic reducing agent tested, accelerating the selective reduction of a naphthyl ketone in water 40-fold when compared with the same reaction using LiBH₄ in methanol. Although the substrates tested in these experiments were completely water-soluble, we have seen that only sparing solubility is necessary to observe hydrophobic effects in the Diels–Alder reaction if one of the components is in water solution.¹² Thus, we expect that the regioselectivity of reduction in the diketones of series **9** in water will also be seen with less soluble substrates using soluble reductants such as the phenyl and pentafluorophenyl borohydrides. Furthermore, the hydrophobic packing involved should also bias the reductions toward diastereoselectivity in appropriate cases.

Table 3. Ratios of Products (10:11) Formed in the Intramolecular Competition Reactions of Quaternized β -Keto Diamines with Substituted Borohydrides under Different Reaction Conditions^{a,b}

	R	D ₂ O	4 M LiCl/D ₂ O	CD ₃ OD
9a	H	46:54	47:53	28:72
9a	Ph	55:45	59:41	35:65
9a	C ₆ F ₅	72:28	77:23	37:63
9b	H	47:53	46:54	33:67
9b	Ph	62:38	67:33	37:63
9b	C ₆ F ₅	90:10	94:6	45:55
9c	H	45:55	45:55	32:68
9c	Ph	60:40	63:37	40:60
9c	C ₆ F ₅	76:24	82:18	46:54

^a Reactions were conducted at a concentration of 8 mM and were carried to ca. 5% reduction of the ketones. ^b All ratios are within an error of ± 1 in at least duplicate runs.

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Supporting Information Available: NMR, MS, and procedures for the synthesis of substituted borohydrides and quaternary salts **5a** and **5b** and **9a**, **b**, and **c**; procedures for competition reactions and samples of ¹H NMR spectra from competition experiments (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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