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MICELLAR PERTURBATION OF ENONE REDUCTION

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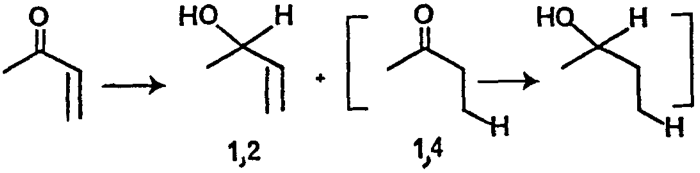
Abstract: The reduction of several enones using BH_4^- in the presence of cationic surfactants has been investigated. These reductions are all shifted by the micelle towards the formation of conjugate reduction products.

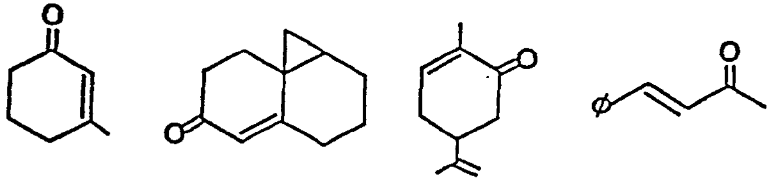
Despite the extensive interest in micellar catalysis of organic reactions, most systems studied to date have focused on simple catalysis of a single well defined process[1]. There are relatively few examples in the literature of preferential micellar enhancement among competing reaction pathways[2]. In this paper, we report preliminary results of experiments where the effect of cationic micelles on the borohydride reduction of enones was studied. We have found that the expected micellar rate enhancement in these systems[3] is accompanied by a substantial shift of the reaction products towards 1,4 reduction. This product shift is consistent for all substrates studied and is in some cases large enough to hold the promise of synthetic utility. It is however, an effect which can be attenuated by the extent and site of micellar solubilization.

In all of our work, the reactions indicated in equation 1 were observed. While we could, in some cases, obtain substantial amounts of ketone product by using only one equivalent of reducing agent, it was never the major product and we found it easier to analyze reactions that used excess reducing agent to yield mixtures of saturated and unsaturated alcohols. While borohydride reductions are routinely conducted in aqueous or alcoholic solvents, our micellar reductions were done in aqueous solutions of cationic hexadecyltrimethylammonium surfactants (typically .01M surfactant). Furthermore, to insure the hydrolytic stability of BH_4^- under the reaction conditions all reactions were .07M in added OH^-. Our study involved a variety of enones in an attempt to test the scope of any micellar perturbation. These compounds are shown in Figure 1. Our initial, and most extensive work was done with 3 methyl-2-cyclohexene-one (I). The results of these experiments are listed in Table I.



(1)

Figure 1: Enone Substrates for BH_4^- Reduction



I **II** **III** **IV**

Our interpretation of the data in Table I involves the following key points. 1) The non-micellar aqueous reactions (entries 1, 2, 7, 8, 11, and 12) all show a strong preference for 1,2 reduction. The micelle containing reactions (entries 3, 4, 5, 6, 9, 10, 13 and 14) *all* show a strong shift towards 1,4 reduction. That is, whether the micelles are provided by added CTAB or by using $CTABH_4$ as the reducing agent, the reaction is shifted from a simple aqueous result of approx. 73% 1,2 reduction to a micellar result of 73% 1,4 reduction. 2) Results in MeOH (entries 15-19) are comparable to non-micellar H_2O results. 3) Addition of non-aggregating tetra-alkyl ammonium salts (entry 2) or the switch from sodium to ammonium counterions (entries 3 vs 14 and 15 vs 17) seem to have little effect on either the H_2O, MeOH or micellar results. A small, but real, perturbation of the product distribution is seen by going from $NaBH_4$ to $(CH_3)_4NBH_4$ to $(nBu)_4NBH_4$ (entries 1, 8, and 12). The softer, more hydrophobic counterions do lead to an increase in 1,4 addition product,[4] but this shift is still small compared to the micelle induced change. Thus, the micellar ammonium counterion to the BH_4^- might be responsible for part, but not all, of the observed effect. 4) The only change in reaction conditions that is able to mimic a micelle product distribution, is a change to iPrOH solvent (entries 20, 21 and 22). This medium virtually matches the extent of 1,4 reduction seen in the micelle. It is interesting to note, however, that while the CTAB and $CTABH_4$ micelles give an overall enhancement of reduction rate[3], under reaction conditions where the micelle reactions yield little, if any, unreacted starting material, the iPrOH reactions are badly incomplete (>70% recovered starting material).[5]

In an attempt to both challenge the micelle's ability to enhance 1,4 reduction and to test for the intervention of an electron transfer pathway in either the micellar or non-micellar reaction, we explored the effect of cationic micelles on the reduction of the cyclopropylcarbinyl enone, **II**.[6] While under no conditions did we see evidence for the ring open rearrangement products that would have suggested the intermediacy of radical anions, we did see a change from ~3% 1,4 reduction in MeOH to >25% 1,4 reduction in micellar CTAB[7].

Experiments with a more water soluble enone, carvone (**III**), allowed us to verify the micelle's ability to overcome a presumably less favorable partition coefficient and also to test the effect of a substituent at the α position of the enone. For this substrate as

Table 1[a]: Reduction of I by BH_4^-: Reaction Conditions and Product Distribution

Entry	Reducing Agent	Solvent	Rxn Time(hrs)	1,4 Prod	1,2 Prod	I	Ratio 1,4:1;2
1	$NaBH_4$[b]	H_2O	15	20	65	14	24:76
2	$NaBH_4$[b]	H_2O/TMAB[d]	15	23	64	12	27:73
3	$NaBH_4$[b]	H_2O/CTAB[e]	18	71	29	—	71:29
4	$CTABH_4$[c,f]	H_2O	11	57	20	24	74:26
5	$CTABH_4$[b,f]	H_2O	24	64	33	4	66:34
6	$CTABH_4$[c,f,g]	H_2O/CTAB[e]	17	68	29	3	70:30
7	$(CH_3)_4NBH_4$	H_2O	18	13	31	57	29:71
8	$(CH_3)_4NBH_4$[c,g]	H_2O	20	17	37	46	31:69
9	$(CH_3)_4NBH_4$[c]	H_2O/CTAB[e]	18	73	24	3	75:25
10	$(CH_3)_4NBH_4$[c,g]	H_2O/CTAB[e]	20	75	23	3	77:23
11	$(nBu)_4NBH_4$[c]	H_2O	17	9	24	67	27:73
12	$(nBu)_4NBH_4$[c,h]	H_2O	17	20	32	49	38:62
13	$(nBu)_4NBH_4$[c]	H_2O/CTAB[e]	17	67	29	4	70:30
14	$(nBu)_4NBH_4$[c,h]	H_2O/CTAB[e]	17	72	26	3	73:27
15	$NaBH_4$[b]	MeOH	15	18	82	—	18:82
16	$(CH_3)_4NBH_4$[c]	MeOH	18	20	74	7	21:79
17	$(CH_3)_4NBH_4$[c,g]	MeOH	20	25	66	9	28:72
18	$(nBu)_4NBH_4$[c]	MeOH	17	17	77	6	18:82
19	$CTABH_4$[c,f]	MeOH	17	18	71	11	20:80
20	$NaBH_4$[c]	iPrOH	17	21	9	70	70:30
21	$(CH_3)_4NBH_4$[c]	iPrOH	17	22	8	70	73:27
22	$(nBu)_4NBH_4$[c]	iPrOH	18	19	7	74	72:28

a) Except where indicated, all reactions were 5×10^{-4}M in substrate (I) and were .07M in added NaOH

b) $[BH_4^-] = 5 \times 10^{-3}$M

c) $[BH_4^-] = 2.5 \times 10^{-3}$M

d) .01M $(CH_3)_4N^+Br^-$

e) .01M Hexadecyltrimethylammoniumbromide

f) Hexadecyltrimethylammoniumborohydride

g) NaOH replaced by $(CH_3)_4NOH$

h) NaOH replaced by $(nBu)_4NOH$

well, the reduction products are shifted from 38% 1,4 reduction to 55% 1,4 reduction. This shift sets a lower limit for the intrinsic micellar effect in this system, since any reaction taking place in the bulk aqueous phase would minimize the observed perturbation of product distribution.

Lastly, we checked the effect of micelles on the reaction of 4 phenyl-3-butene-2-one (**IV**). Our interest was to assess the effect of additional conjugation on the enone and also to see if the presence of an aromatic moiety might attenuate the extent of micellar modification of the reaction product.[8] The observed effect in this case was small, but reproducible. Non-micellar reduction gave 13% 1,4 reduction, compared with 21% 1,4 reduction in the cationic micelles.

We are still attempting to optimize the micelle induced shift in these reaction products and to further elucidate the scope of this effect. Experiments designed to elucidate the source of this micellar perturbation are also in progress and will be reported in due course.

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References and Notes

1) Fendler, J. H.; Fendler, E. J. "Catalysis in Micellar and Macromolecular systems." Academic Press: New York, (1975).

2) For example see: Link, C. M.; Jansen, D. K.; Sukenik, C. N. J. Am. Chem. Soc. (1980), **102**,7798 and references therein.

3) Menger, F. M.; Bonecamp, J. M. J. Am. Chem. Soc. (1981), **103**, 2140.

4) The influence of cation on related reductions has been discussed in: Loupy, A.; Seyden-Penne, J. Tetrahedron (1980), **36**,1937 and references therein.

5) For a comparison of rates of borohydride reductions in different solvents see: Brown, H. C.; Ichikawa, K. J. J. Am. Chem. Soc. (1961), **83**, 4372.

6) The synthesis of **II** and its use to detect radical anion formation by electron transfer is reported in: House, H. O. Accts. Chem. Res. (1976), **9**,59 and references therein.

7) All results reported herein are based on GC analyses of the product mixtures of the isomers of both the saturated and unsaturated alcohols. All products had the expected spectral properties by NMR, IR and MS. The analysis of the products of II was complicated by the fact that while the expected 1,2 product could be characterized, it dehydrated to the cyclopropyl diene on being put through the G.C. This diene was also fully characterized.

8) The question of sites of solubilization of aromatic substrates and a clearer example where a micellar effect is markedly changed by the presence of an aromatic moeity are discussed in: Sutter, J. K.; Sukenik, C. N.; submitted for publication.

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