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ASYMMETRIC REDUCTION OF ARYL TRIFLUOROMETHYL KETONES WITH AN ACHIRAL NADH MODEL COMPOUND IN A CHIRAL HYDROPHOBIC BINDING SITE OF SODIUM CHOLATE MICELLE, β-CYCLODEXTRIN AND BOVINE SERUM ALBUMIN

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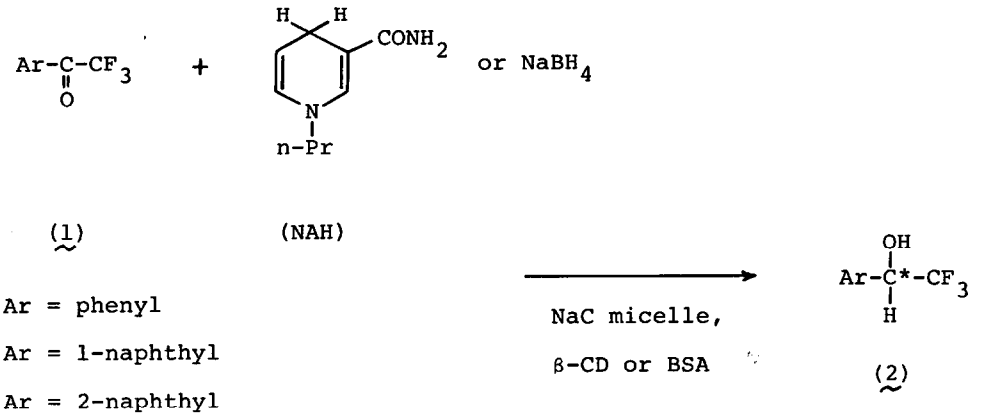
Recent interest in asymmetric reduction has emphasized the exploration of model reactions for stereospecific dehydrogenase-catalysed reduction of carbonyl compounds in the presence of NADH. While the asymmetric reductions bearing on the NADH model have been done by introducing chiral centre(s) exclusively into the 1,4-dihydronicotinamide moiety and/or substrate,[1] there is to date no research with achiral NADH model analogues in a chiral environment. Asymmetric induction of this type has been the subject of much interest in surveying a newer method of asymmetric transformation. The present communication describes an asymmetric reduction of aryl trifluoromethyl ketones ((1a) - (1c)) with a water-soluble 1-propyl-1,4-dihydronicotinamide (NAH) as an achiral NADH model compound in the aqueous solution of sodium cholate (NaC) micelle,[2] β-cyclodextrin (β-CD) and bovine serum albumin (BSA), each of which has a chiral hydrophobic binding site capable of including water insoluble guest ketones. In addition, results on $NaBH_4$ reduction in the same condition were compared with those by NAH.

To a 0.01 M borate buffer solution (pH 9.2) of 1a - 1c (5.0 mM) in the presence of NaC (0.4 M), β-CD (0.05 M) or BSA (1.5 - 1.7 mM)[3] was added NAH (0.025 M) or $NaBH_4$ (0.01 M) and the mixture was stirred at 25°C in the dark for a week. The product alcohol was extracted with ether or trichloroethylene, followed by preparative vpc to give the pure material. The chemical yields in the NAH and $NaBH_4$ reductions were 20 - 60% and quantitative respectively by vpc analysis. From optical rotation of the alcohol the enantiomeric excess was calculated.



(1a): Ar = phenyl

(1b): Ar = 1-naphthyl

(1c): Ar = 2-naphthyl

As shown in the Table, asymmetric induction in the alcohols was obtained with asymmetric bias ranging over 0.6 - 1.4% in NaC micelle, 1 - 10% in β-CD and 16 - 47% in BSA respectively. Although β-CD provided slightly higher enantiomeric excess in the alcohols than NaC micelle, the asymmetric bias are rather small in both systems compared with that observed previously in the asymmetric reduction of 1a with chiral model compounds of NADH (a maximum of 16% enantiomeric excess).[6] The low stereoselectivity might be due to a low chiral environment of their hydrophobic binding sites. In contrast to the above two systems BSA was found to afford much higher optical yields in all the substrates. At present, we do not know how the large asymmetric bias come out in comparing with those by NaC micelle and β-CD. However, it is noted that BSA is a naturally occurring polypeptide with various polar and non-polar groups in the protein molecule, while NaC micelle and β-CD are rather simple aggregate or compound composed of several chiral monomers linked by intermolecular forces or covalent bonds. This fact might be primarily responsible for the large differences in the chirality inducing ability of the hosts described above.

When the two reducing agents of NAH and $NaBH_4$ are compared, the magnitude of asymmetric bias is comparable in the present systems, but the configurations of the alcohols are dramatically reversed with respect to the type of reducing agents except for run 5 and 17. This finding is another interesting example of different behavior of NAH from $NaBH_4$ in stereochemistry, since Pandit found a large difference between the two reducing agents in the stereochemical outcome

Table. Asymmetric Reduction of Aryl Trifluoromethyl Ketones with NAH and $NaBH_4$ in a 0.01 M Borate Buffer Solution of NaC Micelle, β-CD and BSA.

Run	Chiral inclusion system	Ketone (1)	Reducing agent	Alcohol (2) $[\alpha]_D^{25}$	Alcohol (2) Optical yield (%)	Alcohol (2) Configuration
1	NaC	1a	NAH	-0.11	0.7[a]	(*R*)
2	NaC	1b	NAH	-0.11	0.6[b]	(*R*)
3	NaC	1c	NAH	-0.25	0.8[c]	(*R*)
4	NaC	1a	$NaBH_4$	0	0	-
5	NaC	1b	$NaBH_4$	-0.27	1.4	(*R*)
6	NaC	1c	$NaBH_4$	+0.25	0.8	(*S*)
7	β-CD	1a	NAH	-0.62	3.7	(*R*)
8	β-CD	1b	NAH	-0.20	1.1	(*R*)
9	β-CD	1c	NAH	-1.88	5.8	(*R*)
10	β-CD	1a	$NaBH_4$	0	0	-
11	β-CD	1b	$NaBH_4$	+0.48	2.6	(*S*)
12	β-CD	1c	$NaBH_4$	+3.23	10.0	(*S*)
13	BSA	1a	NAH	-6.88	46.6	(*R*)
14	BSA	1b	NAH	-5.65	30.0	(*R*)
15	BSA	1c	NAH	-7.18	22.3	(*R*)
16	BSA	1a	$NaBH_4$	+5.34	36.2	(*S*)
17	BSA	1b	$NaBH_4$	-2.94	15.6	(*R*)
18	BSA	1c	$NaBH_4$	+12.51	38.8	(*S*)

[a]Based on the maximum rotation of (*S*)-phenyltrifluoromethylcarbinol $[\alpha]_D$ +14.76° (benzene) calculated from the data in reference 4. [b]Based on the maximum rotation of (*S*)-1-naphthyltrifluoromethylcarbinol $[\alpha]_D^{25}$ +18.8° (chloroform) calculated from the data in reference 5. [c]Based on the maximum rotation of (*S*)-2-naphthyltrifluoromethylcarbinol $[\alpha]_D^{25}$ +32.2° (chloroform) calculated from the data in reference 5.

on the reduction of 4-t-butylcyclohexylidene iminium salt, i.e., the equatorial attack of hydride is favoured over the axial attack in the case of NAH, while the reverse is observed in the $NaBH_4$ reduction.[7]

The asymmetric reaction reported here can be regarded as a new biomimetic model for NADH dependent reduction in biological systems and it will allow us to control and/or improve the direction and magnitude of the asymmetric induction by suitably modifying NADH model compound or by the use of another proteins and reducing agents.

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References and Notes

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(3) Maximum optical yield was obtained at the concentration of NaC, β-CD or BSA indicated in each parentheses.

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