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ASYMMETRIC REDUCTION OF AROMATIC KETONES BOUND IN THE CHIRAL HYDROPHOBIC INTERIOR OF SODIUM CHOLATE MICELLE

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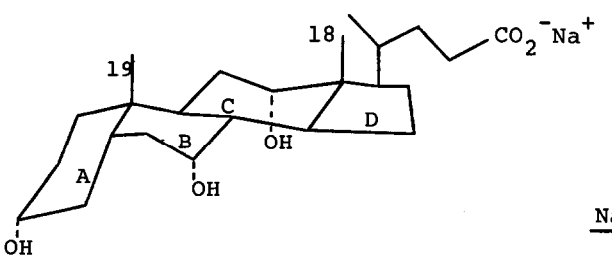
In general asymmetric reactions have been done by covalent attachment of chiral sources to reagents and/or reactants. Recent interest has place in asymmetric reactions effected by non-covalent binding into the chiral interior of chemically-organized inclusion aggregates or compounds. Up to date, such chiral inclusion systems have only been limited to optically active functional micelles and crown ethers, cholesteric liquid crystals and cyclodextrins. In this communication we describe that the micelle formed in solubilization of sodium cholate (NaC), one of bile salts, in water above the critical micellar concentration (ca. 8 mM at 20°C),[1] can serve as another member of chemically-organized inclusion aggregates capable of binding hydrophobic reactants into the chiral inetrior and attaining to asymmetric induction in the subsequent reactions.



NaC

For the present asymmetric reaction we investigated the reduction of aromatic ketones with sodium borohydride ($NaBH_4$) in the micelle. In the presence of NaC in the range of 0.1 - 0.8 M aromatic ketones of (1a) - (1e) (5.0 mM) were solubilized in water with stirring for 6 hrs at 20°C and then reduced with $NaBH_4$

(0.01 M) for 2 hrs. The alcohols were extracted with ether and purified by preparative GLC to give pure materials in a quantitative yield. The optical rotations of the alcohols were measured at 25°C and the optical yields were calculated using the values of optical rotations for the optically pure alcohols (Table I). When alkyl phenyl ketones of acetophenone 1a, isobutyrophenone 1b and tert-butyl phenyl ketone 1c were reduced in the presence of 20 - 160 equivalent moles of NaC, no chirality was introduced into the alcohols. However, in the reduction of naphthyl ketones (1d and 1e) the optically active alcohols were obtained and the optical yields became higher with increasing amounts of NaC to attain to the maximal values of 1.7 and 1.2%, respectively. Essentially no asymmetric induction occurred in the methanol solution where there is no micellar structure,[2] and addition of a competitive guest compound and NaCl also decreased the optical yields of alcohols. For example, in the case of 1d the optical yields were 0.8% in the presence of phenylcyclohexane (5.0 mM) and 1.1% in addition of 0.15 M NaCl where the micelle is composed of 5 NaC salts,[1] respectively.

The binding site of aromatic ketones in the micelle was firmly determined to be the chiral hydrophobic interior on the proton NMR observation that the C-18 and C-19 methyl protons located in this region were strongly perturbed by the diamagnetic anisotropy effects of aryl group in bound aromatic ketones.[3] Both methyl protons gradually shifted upfield with increasing amounts of ketone (5 - 30 mM) in the D_2O solution of NaC (0.2 M). In addition of 30 mM ketone the C-18 and C-19 methyl protons revealed a small upfield of 1.2 and 2.2 Hz for alkyl phenyl ketones, while for acetonaphthones the shifts were larger than for the above system and the C-18 and C-19 methyl protons moved upfield by 3.2 and 7.0 Hz, respectively.[4] The greater shift of the C-19 methyl protons than that of the C-18 methyl protons suggests the preferential binding site near the A/B ring junctures of the steroids.

From the results obtained above we can notice two informative points concerning the asymmetric induction in the NaC micelle, although the micelle serves as a very low chiral environment (optical yield: <2%): (1) *asymmetric induction does occur in the chiral hydrophobic interior of the micelle where guest aromatic ketones are bound*, and (2) *the stereoselectivity is strongly dependent upon the*

Table I. Asymmetric Reduction of Aromatic Ketones[a] with $NaBH_4$[b] in the NaC Micelle at 20°C.

Aromatic ketone	[NaC]/[Ketone][c]	(2)[d] Optical yield (%) (Configuration)
(1a) Acetophenone	20 - 160	0
(1b) Isobutyrophenone	20 - 160	0
(1c) tert-Butyl phenyl ketone	20 - 160	0
(1d) 1-Acetonaphthone	20	1.2 (*S*)
	40	1.7 (*S*)
	80	1.7 (*S*)
	80[e]	0
	80[f]	0.8 (*S*)
	40[g]	1.1 (*S*)
	80[g]	1.1 (*S*)
(1e) 2-Acetonaphthone	20	0.8 (*S*)
	40	1.2 (*S*)
	80	1.2 (*S*)

[a] 5.0 mM. [b] 0.01 M. [c] Molar ratio. [d] The pure alcohols were isolated by preparative GLC ((2a) and (2b): PEG 6000, 1 m, 170°C; (2c), (2d) and (2e): EGSS-X, 1 m, 180°C). Optical yield is defined as $[\alpha]_{D_{obs}}/[\alpha]_{D_{max}} \times 100$ (%). $[\alpha]_{D_{max}}^{23}$ = +45.5° (methanol) for (*R*)-2a (R. Huisgen and Ch. Ruchardt, *Liebigs Ann. Chem.*, 601, 31 (1956)); $[\alpha]_{D_{max}}^{23}$ = +48.3° (ether) for (*R*)-2b (D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, 79, 2866 (1957)); $[\alpha]_{D_{max}}^{20}$ = +36.2° (ether) for (*R*)-2c (R. MacLeod, F. J. Welch and H. S. Mosher, *J. Am. Chem. Soc.*, 82, 876 (1960)); $[\alpha]_{D_{max}}$ = +74.39° (ethanol) for (*R*)-2d (R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1115 (1914)); $[\alpha]_{D_{max}}$ = +41.3° (ethanol) for (*R*)-2e (T. A. Collyer and J. Kenyon, *J. Chem. Soc.*, 676 (1940)). [e] Methanol was used as a solvent in place of water. [f] A competitive guest compound of phenylcyclohexane (5.0 mM) was added. [g] NaCl (0.15 M) was added.

geometrical fitting between the micellar chiral interior and an aryl group in aromatic ketones. The latter point is derived from the fact that in contrast with no asymmetric induction in the alkyl phenyl ketone system regardless of kinds alkyl groups, the ketones with a naphthyl group can be stereoselectively reduced, but the optical yields induced in the alcohols decrease in expansion of the micellar size. The present finding suggests that a host-guest fitting in general plays an important role in asymmetric reactions by the manner of inclusion into the chiral environment.

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References and Notes

(1) The NaC micelle with a small aggregation number of 2 - 4 is strikingly different from micelles formed by detergents. The micellar structure can be crudely depicted as a broad cylinder: the hydrophobic sides of the steroids compose the chiral interior whereas the hydroxy and carboxylate groups project from the outside walls: for a review see M. C. Carey and D. M. Small, *Arch. Intern. Med.*, 130, 506 (1972).

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(4) As a control experiment the two methyl protons shifted by an insignificant amount (0.2 Hz) in methanol, where there is no micellar structure. The induced upfield shift in addition of 0.15 M NaCl was almost same as that in the no NaCl for both phenyl and naphthyl ketone systems. The NMR study could not give an information on the definite structure of ketones bound into the micellar interior.

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