Asymmetric Synthesis in the Oxymercuration Reaction Using Optically Active Mercuric Salts[1)]

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The oxymercuration-demercuration of styrene with optically active mercuric tartrate, 2-phenylpropionate, mandelate, camphorate, menthoxyacetate, and monomethyl tartrate resulted in a partial asymmetric synthesis of 1-phenylethanol. When mercuric tartrate was used, exceptionally high optical yields (25—32%) were observed. The mechanisms for the asymmetric synthesis are discussed.

In many stereochemical investigations of the oxymercuration of olefins, asymmetric syntheses have recently been reported. Partial asymmetric syntheses were achieved in the methoxymercuration of the menthol and sugar esters of $\alpha\beta$-unsaturated acids.[2)] In these investigations, the chiral moiety resided in the olefinic part. As part of an investigation of asymmetric oxymercuration using optically active mercuric salt as a chiral center, Wright[3)] reported that two diastereomeric methoxymercurials were obtained in unequal amounts by the methoxymercuration of cyclohexene with mercuric (+)-lactate. After we had presented the results of asymmetric oxymercuration which would be included in the present paper, Carlson and Funk[4)] reported similar results using decene, octene, heptene, and allylbenzene as the olefinic substrates. However, the author did not refer to the stereochemical reaction mechanisms at all.

The present paper will deal with the results of the asymmetric synthesis of 1-phenylethanol (**3**) *via* the oxymercuration of styrene (**1**) with mercuric salts of chiral acids, utilizing the convenient and mild oxymercuration-demercuration procedure developed by Brown.[5)]

Styrene (**1**) was subjected to an oxymercuration reaction with an equivalent amount of mercuric salts in 50% aqueous tetrahydrofuran (THF) at 25 °C, and the resulting oxymercurials were submitted to demercuration *in situ* with alkaline sodium borohydride. The resulting **3** was purified by means of fractional distillation and, in some cases, by preparative vapor phase chromatography (vpc). The possibility of racemization of the reaction products during demercuration was safely excluded by the confirmation of the constant optical purity of chiral **3** in an alkaline medium. The results are summarized in Table 1.

$$\underset{(1)}{C_6H_5\text{-}CH{=}CH_2} \xrightarrow[H_2O\text{-}THF]{Hg(OCO\overset{*}{R})_2\ (2)} \xrightarrow{NaBH_4} \underset{OH\quad (3)}{C_6H_5\text{-}\overset{*}{C}H\text{-}CH_3}$$

As is shown in Table 1, an exceptionally high optical yield of **3** was observed when mercuric tartrate (**2a**) was used. On the contrary, the other chiral mercuric salts (**2b-g**) gave very low or no measurable optical yields.

It is well known in oxymercuration that the addition of perchloric acid or Lewis acids such as boron trifluoride effectively accelerates the reaction. Inouye[2a)] reported that the methoxymercurations of (−)-menthyl crotonate, cinnamate, and β-methylcinnamate were accelerated by boron trifluoride etherate, and that the optical yields of these reactions were comparable to those without the catalyst. In the present system, the addition of boron trifluoride accelerated the reaction; however, only a slight asymmetric induction was achieved and the predominant product was (−)-**3**, which was enantiomeric to that without the catalyst.

The role of the acid catalyst is looked upon as promoting the dissociation of mercuric salts leading to the highly active acyloxymercuric cation, which then added to the olefin to yield the mercurinium ion.

$$(RCOO)_2Hg \overset{H^+}{\rightleftharpoons} RCOOHg^+ + RCOOH$$

$$\text{>C=C<} + RCOOHg^+ \rightleftharpoons \text{C(HgOCOR)C}$$

The chiral environment which the mercury atom of the mercuric tartrate cation, HOOC·CHOH·CHOH·COOHg$^+$, experiences seems to be similar to that of mercuric methyl tartrate (**2g**). Therefore, it is conceivable, on the basis of assumptions described above, that low asymmetric induction was observed in either case.

On the other hand, the oxymercuration proceeds very smoothly in methanol solvent, under such neutral conditions, the dissociation of usual mercuric salts cannot be considered so favorable, and the reacting species seems not to be the acyloxymercuric cation but mercuric salt itself. In this case, a molecular adduct

$$\text{>C=C<} + Hg(OCOR)_2 \rightleftharpoons \text{C(Hg(OCOR)}_2\text{)C} \rightleftharpoons \text{C(HgOCOR)C}$$

or π-complex is formed at first, and the configuration of the product is determined at this stage if the product is formed by the attack of the solvent molecule in *trans* fashion on the π-complex or mercurinium ion formed subsequently, as is generally accepted. The oxymercuration with **2a** was very slow as compared with the reaction using the other salts such as **2b**. This fact also seems to indicate that the tartrate anion

Table 1. Syntheses of optically active 1-phenylethanol (3) by oxymercuration-demercuration reaction

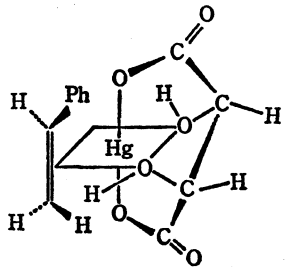
Mercuric salt	Reaction condition[a] Time	3 Yield	3 α_D[b]	3 Opt. yield[c]
(+)-Tartrate (2a)	4 day[d]	4%	+5.64°	25.6%
(+)-Tartrate (2a)	7	5	+5.66	25.7
(+)-Tartrate (2a)	7.5	17	+6.66	30.3
(+)-Tartrate (2a)	14	20	+6.54	29.7
(+)-Tartrate (2a)	14[e]	15	+7.04	32.0
(+)-Tartrate (2a)	28	29	+5.69	25.9
(+)-Tartrate (2a)	1[f]	8	−0.02	0.1
(−)-2-Phenylpropionate (2b)	15 min	40	−0.10	0.5
(+)-Mandelate (2c)	15 hr	70	+0.05	0.2
(−)-Malate (2d)	3	64	±0.00	—
(+)-Camphorate (2e)	24	59	−0.54	2.5
(−)-Menthoxyacetate (2f)	15 min	40	−0.10	0.5
(+)-Monomethyl tartrate (2g)	10	61	+0.09	0.4
Acetate (2h)	15[g]	73	−0.06	0.3
Acetate (2h)	5[h]	62	−0.08	0.4

a) The reaction was carried on at 25 °C. b) The optical rotations were measured as pure liquid using 0.5 dm cell. c) Calculated from the value of α_D^{17} −11.0° (neat, l=0.25 dm): E. Downer and J. Kenyon, *J. Chem. Soc.*, **1939**, 1156. d) When the reaction was carried out for 1 day, no **3** was obtained. e) Under nitrogen atmosphere. f) BF_3-etherate (5 ml) was added. g) Equivalent amount of (+)-diethyl tartrate was added. h) Five equivalent amounts of (+)-diethyl tartrate were added.

strongly combines with mercury, and that the **2a** molecule adds to the olefinic double bond, making a molecular complex.

It is also interesting to note that the oxymercuration with mercuric acetate (**2h**) in a solvent containing (+)-diethyl tartrate produced asymmetric induction to some extent. Henbest[6] reported that, in the methoxymercurials obtained from 4-cyclohexenol and its derivatives, the mercury atom was oriented *cis* relative to the hydroxyl substituent, and he suggested that the coordination between the mercury atom and the substituent oxygen determined the stereochemical course of the addition. Although the complex-forming tendency of mercury toward oxygen is usually considered to be rather weak, it may be suggested that the glycol structure operates to endow a chiral environment to the mercury atom. Consequently, the mercury atom of **2a** becomes chiral by salt forming bonds as well as by coordinating bonds between mercury and hydroxyl oxygen, and it is likely that the complex-formation between **2a** and **1** is the stage of asymmetric synthesis.

When the mercury atom of **2a**, already coordinated by two carboxyl and two hydroxyl groups, makes a molecular complex with olefin, the mercury should have a coordination number more than four. Although



(4)

the tetrahedral four-coordination is more common for mercury complexes, the six-coordinated mercury was suggested in an aqueous solution[7] and octahedral complexes of the type $(HgL_6)(ClO_4)_2$ were obtained when the donor atom was oxygen.[8] If octahedral six-coordination is assumed for mercuric (+)-(*R*,*R*)-tartrate (**2a**), the molecular complex of **2a** and **1** can be depicted as **4**, in which **1** favorably coordinates in the sterically less-hindered orientation. Mercuric (+)-tartrate (**2a**) in **4** has a C_2 chirality as a whole. Chiral complexes are usually more effective than simple chiral atoms in asymmetric inductions. It seems, therefore, to be a natural outcome that **2a** produces exceptionally high optical yields compared with **2b–g**, which is seemingly incapable of forming such a chiral complex. The S_N2-like attack of water on **4** or on the mercurinium ion derived from **4** gives (+)-(*R*)-**3**, which is the predominant isomer actually obtained. The results with **2a** reported by Carlson[4] are consistent with this mechanistic assumption.

Experimental

All the boiling and melting points are uncorrected. The optical activity measurements were carried out on a Zeiss polarimeter and a Yanagimoto ORD-185 recording spectropolarimeter.

Materials. Commercially-available (+)-tartaric acid, (−)-malic acid (mp 105.5—106.5 °C; $[\alpha]_D^{20}$ −1.48°, c=8.29, H_2O), and (+)-camphoric acid (mp 189—193 °C; $[\alpha]_D^{20}$ +47.8°, EtOH) were used without further purification. (+)-Mandelic acid (mp 134—134.5 °C; $[\alpha]_D^{20}$ +155.3°, H_2O) and (−)-2-phenylpropionic acid[9] (bp 133—135 °C/6 mmHg; $[\alpha]_D^{21}$ +73.1°, $CHCl_3$) were obtained by the resolution of each racemic acid with cinchonine and (−)-1-phenylethylamine respectively. (−)-Menthoxyacetic acid[10] (bp 161—169 °C/7 mmHg; $[\alpha]_D^{20}$ −94.9°, MeOH), (+)-methyl hydrogen tartrate[11] (mp 54.5—55.5 °C (monohydrate); $[\alpha]_D^{18}$ +14.7°,

c=21, H_2O), and (+)-diethyl tartrate (bp 140—141 °C/7 mmHg; $[\alpha]_D^{20}$ +7.66°, neat) were prepared by the known procedures. Some of these acids were not completely optically pure; however, the optical purities of the resulting **3** are listed in Table 1 without corrections.

Styrene and THF were distilled before use in each experiment.

Preparations of Mercuric Salts. (+)-Tartaric acid (50.0 g, 0.33 mol) in 150 ml of water was added slowly to a stirred clear solution of mercuric acetate (95.7 g, 0.30 mol) in 400 ml of water. After the mixture was stirred for a while, the resulting white precipitates were washed with water until the filtrate became neutral. After drying under reduced pressure, 98.2 g (94%) of mercuric (+)-tartrate (**2a**) were obtained. Mp>200 °C, no clear mp indicated. Found: Hg, 57.7%. Calcd for $C_4H_4O_6Hg$: Hg, 57.5%.

Mercuric (−)-2-phenylpropionate (**2b**); mp 94—95 °C (recrystallized from EtOH); $[\alpha]_D^{24}$ −59.1° ($CHCl_3$); yield, 70.2%. Found: Hg, 39.0%. Calcd for $(C_9H_9O_2)_2Hg$: Hg, 40.2%. Mercuric (+)-mandelate (**2c**); mp 172—172.5 °C; yield, 95.3%. Found: Hg, 39.9%. Calcd for $(C_8H_7O_3)_2Hg$: Hg, 39.9%. Mercuric (−)-malate (**2d**); mp>200 °C, no clear mp indicated; yield, 86.5%. Found: Hg, 57.2%. Calcd for $C_4H_4O_5Hg$: Hg, 60.3%. Mercuric (+)-camphorate (**2e**); mp 266 °C (decomp.); yield, 95.6%. Found: Hg, 49.3%. Calcd for $C_{10}H_{14}O_4Hg$: Hg, 50.3%. Mercuric (−)-menthoxyacetate (**2f**); mp 64—66 °C (recrystallized from EtOH-H_2O), $[\alpha]_D^{20}$ −59.8° ($CHCl_3$); yield, 66.8%. Found: Hg, 30.8%. Calcd for $(C_{12}H_{21}O_3)_2Hg$: Hg, 32.0%. Methyl mercuric (+)-tartrate (**2g**); mp 171—172 °C (decomp.); $[\alpha]_D^{18}$ +27.4° (H_2O); quantitative yield. Found: Hg, 35.7%. Calcd for $(C_5H_7O_6)_2Hg$: Hg, 38.1 %; for $(C_5H_7O_6)_2Hg\cdot 2H_2O$: Hg, 35.6%.

Analysis of Mercury. Adams' procedure[12] was modified. To 0.2 g of the mercuric salt were added 10 ml of 7% fuming sulfuric acid and 5 ml of fuming nitric acid. The mixture was heated until reflux, and to it was added water sufficient to dissolve the mercuric salt. Refluxing was continued with the addition of water in small portions until the evolution of NO_2 gas ceased. To the cooled, colorless, clear solution was added 1 drop of 4% potassium permanganate solution, the color of which persisted for 5 min. The excess permanganate was removed by means of 5% ferrous sulfate solution. The mercury in the prepared sample was titrated with 0.05 N KSCN solution, using ferric alum as an indicator (Volhard method).[13]

General Method of Oxymercuration-demercuration. Mercuric (+)-tartrate (**2a**, 17.5 g, 50.2 mmol) was suspended in 50 ml of water, to which was added 50 ml of THF. Styrene (**1**, 5.23 g, 50.2 mmol) was then added dropwise to the suspension under well-stirring at 25 °C, and the reaction mixture was stirred in dark at that temperature for 7.5 day. To the mixture were added 50 ml of 3.0 M NaOH and then sodium borohydride (0.90 g, 23.8 mmol) in 50 ml of 3.0 M NaOH, and the mixture was stirred for 15 min. The resulting metallic mercury was filtered off and the filtrate was saturated with NaCl and extracted with ether. The ether extract was washed with water and dried over Na_2SO_4. Distillation under reduced pressure gave 1.03 g (16.8%) of crude **3** (bp 84—85 °C/8 mmHg, n_D^{20} 1.5292), which contained **1**, acetophenone, benzaldehyde, and benzyl alcohol up to a total of 5%. The crude product was purified by preparative vpc (PEG-20M 25% on C-22 fire-brick, 3 m column), and submitted to optical rotation measurements, α_D^{20} +6.66° (neat, l=0.50 dm). The product was identified by elemental analysis and by comparisons of the vpc retention time and the IR and NMR spectra with those of an authentic sample.

In the cases of **2b**, **2c**, **2e**, and **2f** the starting acids were recovered without racemization from the aqueous layer of ether extraction.

*Treatment of **3** in an Alkaline Medium.* (+)-1-Phenylethanol (**3**, α_D^{19} +6.41°, neat, l=0.50 dm; 0.61 g) was stirred with 20 ml of 3.0 M NaOH, 10 ml of water, and 10 ml of THF at 25 °C for 19 hr. After work-up and distillation, 0.40 g of **3** (α_D^{19} +6.40°, neat, l=0.50 dm) was recovered.

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