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THE CATALYTIC HYDROGENOLYSIS OF BENZYLAMINE DERIVATIVES

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Abstract—The hydrogenolysis of optically active ethyl 2-amino-2-phenylpropionate (I), its N-methyl (II), and N,N-dimethyl (III) derivatives was studied using Raney Ni and Pd as the catalysts. The Raney Ni catalysed hydrogenolysis of II and III, as well as the reaction catalysed by Pd, occurred predominantly with inversion of configuration; this is not in accord with the hydrogenolysis of corresponding benzyl alcohols. This difference can be ascribed to the difference of the affinity for Ni between N and O atoms. The "S_Ni" process may be inhibited in the Raney Ni catalysed hydrogenolysis of II and III since the amino group acts as a self-catalyst poison, and the "S_N2" process appears to be preferable to the "S_Ni" one. The predominance of the configurationally inversion was also observed in the Pd catalysed hydrogenolysis of I. These results over Pd are reasonable in reflecting that the N atom has not so high affinity for Pd. The hydrogenolysis of a quarternary ammonium bromide of I was also reported.

INTRODUCTION

There have been many reports on the stereochemistry of catalytic hydrogenolysis of benzyl derivatives.[1-7] However, previous investigations in this field have dealt mostly with the hydrogenolysis of benzyl alcohol derivatives, and there have been only a few reports[2,3,7] on those of benzylamine derivatives. In 1965, Mitsui and Sato[3] reported the hydrogenolysis of ethyl 2-amino-2-phenylpropionate (I), methyl 2-anilino-2-phenylpropionate (V), and 2-anilino-2-phenylpropionic acid (VI). However, the configurations of V and VI were unknown at that time. Recently, Dahn *et al*[7] have also reported the hydrogenolysis of some 2-amino-2-phenylpropionic acid derivatives including VI, and confirmed the configuration of VI. These reports[7] prompted us to further investigate the hydrogenolysis of benzylamine derivatives. In this paper, we describe the hydrogenolysis of some optically active 2-amino-2-phenylpropionic acid derivatives, and discuss the mechanism of this hydrogenolysis.

RESULTS

The ethanol solutions of optically active ethyl 2-amino-2-phenylpropionate (I), ethyl 2-methylamino-2-phenylpropionate (II), ethyl 2-dimethylamino-2-phenylpropionate (III), or quarternary ammonium bromide of I (IV) were hydrogenated over Raney Ni and Pd, 5% on charcoal, under ordinary pressure of hydrogen, and the mixtures were analyzed by gas chromatography. The product distributions are shown in Table 1. Table 2 summarizes the stereospecifity of the hydrogenolysis of the C—N bond, which was calculated from the optical rotation of ethyl 2-phenylpropionate (VII).

In the Raney Ni catalysed hydrogenation of I at 50°, selective saturation of the Ph group, and/or carbethoxy group were observed, and the C—N bond was not hydrogenolysed to any extent (Run 1). This is consistent with the reports by Mitsui and Sato,[3] and by Bonner and Zderic.[4c] Compound II was hydrogenated over Raney Ni to the mixture of VII (51%), ethyl 2-methylamino-2-cyclohexylpropionate (42%), *etc* at 50°, and the configuration of VII was inverted stereospecifically (Run 3). The hydrogenolysis of III yielded selectively VII with stereospecific inversion (Run 5). Compound IV was hydrogenolysed over Raney Ni with evolution of hydrogen, and the configuration of VII was racemised completely (Run 7).

Pd catalysed hydrogenation of I at 50° gave the mixture of VII (89%) and ethyl 2-amino-2-cyclohexylpropionate (11%), and the configuration of VII was inverted predominantly (Run 2). This is not in accord with the Mitsui and Sato's finding[3] that the slightly-predominant retention of configuration occurred in the hydrogenolysis of I at 150° and 60 atm. The selective hydrogenolyses over Pd were observed in II and III (Runs 4 and 6). In these cases, the inversion of configuration of VII occurred predominantly. Murchu[7] also reported the inversion of configuration in the hydrogenolysis of III. Moreover, the hydrogenolysis of IV was accompanied by the predominant inversion (Run 8).

DISCUSSION

Mitsui *et al*[1] reported that the hydrogenolysis of the benzyl alcohols and their methyl ethers over Raney Ni was accompanied by the stereospecific

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Table 1. The hydrogenolysis of ethyl 2-amino-2-phenylpropionates
Product distribution

Run	Substrate	Catalyst (g)	Temp (C°)	Products (%)* VII	A	B	C	D
1	I	Ra Ni 10**	50	4	trace	7	63	26
2	I	5% Pd–C 1·0	50	89	–	–	11	–
3	II	Ra Ni 10**	50	51	1	6	42	–
4	II	5% Pd–C 1·0	50	100	–	–	–	–
5	III	Ra Ni 5**	25	100	–	–	–	–
6	III	5% Pd–C 0·5	25	100	–	–	–	–

Substrate: 1/200 mol., Solvent: EtOH, 50 ml., Under ordinary pressure.

*A: Ethyl 2-cyclohexylpropionate, B: 2-Phenylpropanol, C: Ethyl 2-amino-2-cyclohexylpropionates, D: 2-Amino-2-cyclohexylpropanols.

**Wet weight with EtOH.

Table 2. The hydrogenolysis of ethyl 2-amino-2-phenylpropionate derivatives
Stereochemistry

Substrate					Product (VII)			
Run	Compound	Optical purity (%)	Catalyst (g)	Temp (C°)	Configuration	Optical purity (%)	Stereospecificity (%)	Stereochemistry
1	R(−)-I	40·2	Ra Ni 10	50	–	–	—	—
2	R(−)-I	40·2	5% Pd–C 1·0	50	S(−)	20	50	Inversion
3	S(+)-II	89·0	Ra Ni 10	50	R(+)	88	99	Inversion
4	R(−)-II	46·5	5% Pd–C 1·0	50	S(−)	25	54	Inversion
5	S(+)-III	89·5	Ra Ni 5	25	R(+)	82	92	Inversion
6	R(−)-III	40·2	5% Pd–C 0·5	25	S(−)	21	53	Inversion
7	S( )-IV	89·5	Ra Ni 5	25	(±)	0	0	Racemization
8	S( )-IV	89·5	5% Pd–C 0·5	25	R(+)	36	40	Inversion

Substrate: 1/200 mol., Solvent: EtOH, 50 ml., Under ordinary pressure.

retention of configuration, whereas the stereospecific inversion was observed over Pd catalysts. However, the benzylphenyl thioethers gave the racemic products over Raney Ni and Pd catalysts.[1b,4a] Based on these results, they proposed the mechanism of the catalytic hydrogenolysis of benzyl derivatives,[1] which involves the adsorption of the substrate, the formation of π-benzyl complex, and its decomposition by a chemisorbed hydrogen. π-Benzyl complexes, 3 and 7, will be formed from different adsorbed substrates, 1 and 5, respectively, and, then, decomposed by chemisorbed hydrogen with configurational retention. The hydrogenolysis with retention proceeds *via* 1 ("S_Ni" process), while the inversion process occurs *via* 5 ("S_N2" process). These processes may be occurring competitively, and the stereospecifity can be ascribed to the free-energy difference at the transition states, 2 and 6; this difference depends on the catalyst, substituent X, additives, and/or solvents. Further, racemization, i.e. stereoconvergent hydrogenolysis proceeds to complex formation *via* radical and/or carbonium ion.[10] This process probably occurs extensively when substituent X has a very high affinity for the catalyst enough to act as a catalyst poison.

Considering the processes discussed above, we can now rationalize the hydrogenolysis of benzyl alcohols and benzylthioethers as follows: Ni has a high affinity for the O atom. The free-energies of the adsorbed substrate 1 and the transition state 2 will be lowered by the strong chemisorption of OR group over Raney Ni; the hydrogenolysis through path 1, which results in the configurational retention, must be preferable to that through path 2. Pd, however, has a low affinity for the O atom. A stereoelectronic factor may be so operating for the Pd catalysed hydrogenolysis. Consequently, path 2, which is accompanied by the inversion of configuration, must be more favorable than path 1. The S atom is a well known catalyst poison. The C—S bond of the thioethers may be cleaved into radical leading to the racemic product.

The affinity of the N atom for Ni lies between

that of O and S atoms. Therefore, it is expected that the hydrogenolysis of the C—N bond over Raney Ni occurrs through paths 1 and/or 3 to give configurationally retained and/or racemic products. But, in fact, the stereospecific inversion of configuration was observed in the hydrogenolysis of II and III over Raney Ni. We can now ascribe this discrepancy to the "self-catalyst poison" of the N atom. These C—N bonds have not such high strains as that of aziridine, and the affinity of the N atom for Ni is less than that of the S atom. Consequently, scarcely any C—N bonds of I, II, and III may be expected to cleave into radicals. Since the chemisorption of the amino groups will rise, the work function of the catalyst – the nucleophilicity of the catalyst will be reduced. Here, the nucleophilicity will decrease more in the neighborhood of the adsorbed nitrogen. The activation energy *via* the adsorption state 1 will rise by the chemisorption of the substrate; scarcely any reaction *via* this state will occur. However, the nucleophilicity in the alternative adsorption 5 will be less decreased than that in 1. Consequently, π-benzyl complex formation *via* 5 must be less inhibited than that via 1, and the hydrogenolysis of II and III occurrs stereospecifically with inversion of configuration. On the other hand, the OR group has such a moderate affinity for Ni that the hydrogenolysis over Raney Ni may be accompanied by the retention of configuration.

The ease of the hydrogenolysis of the amino groups increases in the sequence: I < II < III, as shown in Table 1. Since the catalyst hindrance of the amino group will increase with increasing the number of the Me groups, the adsorption will decrease in the sequence: $NH_2 > NHMe > NMe_2$. Therefore, the nucleophilicity of the catalyst will be reduced in the opposite sequence. The increase in the number of the Me groups will promote the strain release to form the π-benzyl complex. For these reasons, the ease of hydrogenolysis is expected to increase in the order: I < II < III.

The slight predominance of configurational retention was observed in the Raney Ni catalysed hydrogenolysis of styreneimines: 2-methyl- and 1,2-dimethyl-2-phenylaziridines.[2] These differences in the styreneimines and the 2-amino-2-phenylpropionates may be due to the strains of the C—N bonds. The styreneimine has the high reactivity because of its high strain. The C—N bond will be weakened by the adsorption of the nitrogen and the phenyl group. Accordingly, the hydrogenolysis of styreneimine will occur competitively through paths 1 and 3 as previously discussed.[2]

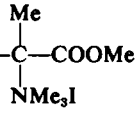
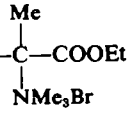
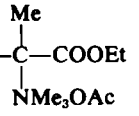
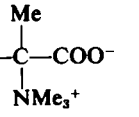
The Pd catalysed hydrogenolysis of benzylamines: I, II, and III occurred with predominant inversion of configuration; these results agree with the cases of benzyl alcohols.[1] Since Pd has not so high an affinity for the N atom,† the relative rates of π-benzyl complex formations *via* 1 and 5 may be mainly governed by the stereoelectronic factor, and the hydrogenolysis proceeds predominantly through path 2. The stereospecifities were lower than those of Raney Ni catalysed hydrogenolysis. These suggest that the nucleophilicity of Pd is not affected so significantly by the adsorption of the amino groups. Mitsui and Sato,[3] however, have reported that the hydrogenolysis of I over Pd at 150° and 60 atm occurred with slightly-predominant retention of configuration; this is not in accord with the above results. Since the reaction conditions are considerably severe in this case, the hydrogenolysis probably proceeds *via* a different process. A possible mechanism involves the formation of a certain bond between the amino group and Pd, followed by the subsequent hydrogenolysis through a process similar to path 1.

In 1965, we showed that the hydrogenolysis of (+)-methyl 2-anilino-2-phenylpropionate (V) over Pd gave S(+)-methyl 2-phenylpropionate (VIII), whereas R(−)-VIII was obtained from (+)-V over Raney Ni.[3] (+)-2-Anilino-2-phenyl-propionic acid (VI), however, was hydrogenolysed to S(+)-2-phenyl-propionic acid (IX) over Raney Ni and Pd.[3] Recently, Dahn *et al* have confirmed that (+)-V and (+) VI have the S configurations.[7] Therefore, the Pd catalysed hydrogenolysis of V and VI occurrs with predominant inversion of configuration; these results agree with those of I, II, and III. The hydrogenolysis of V over Raney Ni, on the other hand, gives mainly the configurationally retained product, but VI is hydrogenolysed predominantly with inversion of configuration. Because the anilino group has a relatively high catalyst hindrance, its inhibitory effect on the hydrogenolysis is considered to be less significant than that of the amino group; the hydrogenolysis of V over Raney Ni proceeds predominantly with retention of configuration. However, the formation of the innersalt of VI will weaken the adsorption of the N atom; the hydrogenolysis of VI results in the configurational inversion. The predominance of inversion was observed in the Raney Ni catalysed hydrogenolysis of ethyl 2-phenoxy-2-phenylpropionate (X).[9] These differences between V and X are probably responsible for the differences of affinity for Ni.

Table 3 summarizes the hydrogenolysis of quarternary ammonium compounds.[7,10] These results may be reasonable in reflecting the order of affinity of the catalyst for the anion: $I^- > Br^- > OAc^-$, COO^-. The racemization during the hydrogenolysis of the iodide (XI) is considered to occur through path 3 on account of the high affinity of the iodide for Pd. The Raney Ni catalysed hydrogenolysis of the bromide (IV) can be explained similarly.

†This is also supported by the fact that the anchor effect of the amino groups is not observed in the hydrogenation of methylcyclohexenylamines.[8]

Table 3. The hydrogenolysis of quarternary ammonium compounds

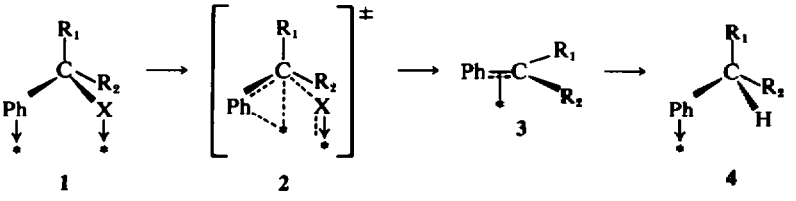
	Substrate	Catalyst	Configuration of product: Retention	Inversion	Ref.
XI		10% Pd-C	50%	50%	7a, b
V		5% Pd-C Ra Ni	30 50	70 50	This work
XII		5% Pd-$BaSO_4$	17	83	10
XIII		5% Pd-$BaSO_4$	9	91	10

Solvent. EtOH for V and XI, EtOH-Et_3N for XII and XIII. Under ordinary pressure and at room temperature.

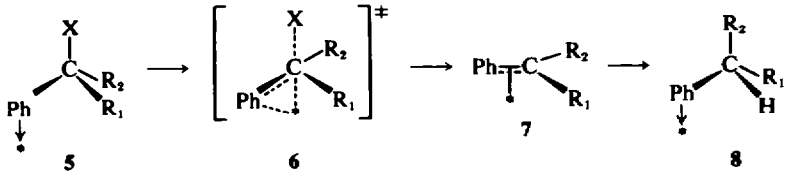
However, IV, the acetate (XII), and the betain (XIII) must be hydrogenolysed mainly through path 2 since these groups have not such high affinities for Pd as the iodide.

EXPERIMENTAL

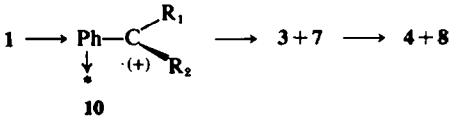
S(+)- and R(−)-Ethyl 2-amino-2-phenylpropionates (I) were prepared by the procedures as previously described.[2]



(1)



(2)



(3)

S(+)-Ethyl 2-methylamino-2-phenylpropionate (II). Sodium hydride (3 g; wet with n-hexane) was added with stirring to S(+)-ethyl 2-formylamino-2-phenylpropionate (5·4 g, $[\alpha]_D^{26}+21·0°$ (*c* 4·77, EtOH))[11] in benzene (300 ml) under a N_2 atm, and the suspension was, then, allowed to stand overnight. A large excess of MeI (15 ml) was added to the suspension at room temp. After the absence of unreacted formamide had been confirmed by gas chromatography,* water (500 ml) was added to the suspension. The organic layer was separated and dried over Na_2SO_4. After the removal of benzene *in vacuo*, the oily residue was dissolved in EtOH (100 ml), and dry HCl was saturated at 0°. Then, the soln was heated under a reflux for 2 hr. The EtOH was removed *in vacuo*, and aqueous ammonia was added to the residue. The suspension was extracted with ether, and the etheral soln was dried over Na_2SO_4. Evaporation of ether and the subsequent distillation gave S(+)-II, 4·0 g (83·3%), bp 134–136°/15 mmHg, $[\alpha]_D^{26}+26·9°$ (*c* 9·72, EtOH). (Found: C, 69·51; H, 8·52; N, 6·65. Calcd. for $C_{12}H_{17}O_2N$: C, 69·54; H, 8·27; N, 6·76%).

S(+)-Ethyl 2-dimethylamino-2-phenylpropionate (III). S(+)–I (10·0 g, $[\alpha]_D^{25}+26·3°$ (*c* 9·45, EtOH)), 37% formalin (11 ml), and Raney Ni (10 g; wet with EtOH) in EtOH (200 ml) were agitated with H_2 at 25° and 1 atm. After 4 hr, the theoretical amount of H_2 was absorbed. The catalyst was filtered off, and the EtOH was removed *in vacuo*. The oily residue was distilled to give S(+)–III, 10·5 g (94·0%), bp 130–133°/12 mmHg, $[\alpha]_D^{25}+10·9°$ (*c* 2·10, EtOH). (Found: C, 70·53; H, 8·67; N, 6·35. Calcd. for $C_{13}H_{19}O_2N$: C, 70·53; H, 8·65; N, 6·28%.

Quarternary ammonium bromide of S(+)–I (IV). The EtOH soln of S(+)–III (1·1 g, $[\alpha]_D^{25}+10·9$ (*c* 2·10, EtOH)), and MeBr (3 ml) was allowed to stand in a sealed tube for 3 weeks at room temp. After the evaporation of EtOH *in vacuo*, S–IV was obtained as an oily syrup, and submitted for the hydrogenolysis experiment without further purifications.

Catalysts. W–4 Raney Ni was prepared by the method of Adkins *et al*[12] shortly before use. Pd, 5% on charcoal, was prepared according to the literature.[13]

Hydrogenolysis. The substrate (1/200 mol) and the catalyst in EtOH (50 ml) was agitated under ordinary pressure of H_2 and at appropriate temp. After the H_2 uptake had ceased, the mixture was analysed by gas chromatography. The analysis was carried out by a Shimadzu 5AP Gas Chromatograph equipped with a column of Carbowax 6000, 5% on Celite 545 (3 mm × 1·5 m), at 140°. The catalyst was filtered off and washed several times with EtOH. The combined filtrates were concentrated, and the residue poured into water and extracted with ether. The ether extract was washed with 4N HCl, and, then, with sat $NaHCO_3$aq, and dried over Na_2SO_4. The evaporation of ether and subsequent distillation afforded VII: bp 104–107°/22 mmHg. In the Raney Ni catalysed hydrogenolysis of II, a small amount of 2-phenylpropanol, which was formed by the reduction of carbethoxy group of VII, was also detected in addition to VII. In this case, VII was purified by preparative gas chromatography. (Column: Carbowax 6000, 5% on Celite 545 (10 mm × 1·5 m), temp 140°) The optical rotation of VII was measured in EtOH at c = 9 − 10. For the rotation of optically pure S(−)–VII, we adopted $[\alpha]_D-72·2$ (EtOH).[14]

*The analysis was carried out by a Hitachi K-53 or F-6 Gas Chromatograph equipped with a Carbowax Golay column (0·5 mm × 15 m) at 180°.

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