Stereospecific Hydrogenations Using Palladium-on-Silica Gel Catalysts

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Studies have been conducted on the stereospecific nature of catalysts prepared by depositing palladium upon silica gels which have been precipitated in the presence of optically active alkaloids. So far, only the gels formed in the presence of the cinchona alkaloids have proved to be active as carriers for asymmetric catalysts. The substrate for this work was α-methylcinnamic acid affording a slight excess of (+)-dihydro-α-methylcinnamic acid on reduction. Details of the preparation of the carriers and catalysts and studies made on their stereoselective properties are given.

In an earlier paper Beamer, *et al.* (1), presented evidence supporting the existence of substrate-specific and stereospecific centers in palladium-on-carbon catalysts. These data were in accord with the three-point contact theory proposed by Ogston (2) to explain stereospecificity in enzymes. This work also indicated the possible design of an asymmetric synthesis resembling those catalyzed by enzymes but using a nonbiologic catalyst such as palladium. That such a synthetic reaction is not impossible is evidenced by the work of Akabori with palladized silk fibroin (3) and Smith using specially treated palladized charcoal (4).

The present work is concerned with further studies into the stereospecific hydrogenations catalyzed by certain palladized silica gels (5). The gels used in these experiments were prepared by precipitation from a sodium silicate solution using hydrochloric acid in the presence of the various alkaloids of the cinchona family. Although other alkaloids have been employed in these experiments (strychnine, brucine, ephedrine, and monobenzoylephedrine), so far only the gels prepared with the cinchona alkaloids have proved to be active as carriers for asymmetric catalysts. The substrate for this work was α-methylcinnamic acid affording a slight excess of (+)-dihydro-α-methylcinnamic acid on reduction. Oximes such as acetophenone oxime, α-oximinopropiophenone, and 3-pentyl-*p*-methoxyphenylketoxime either could not be reduced using these catalysts or upon reduction produced optically inactive products.

Prior to our work, Dickey (6) and Haldeman and Emmett (7) had demonstrated adsorption specificity and Beckett and Anderson (8) had shown stereoselective adsorption on similarly prepared gels.

EXPERIMENTAL

Reagents.—α-Methylcinnamic acid (K and K Laboratories), quinine sulfate N.F., quinidine sulfate U.S.P., cinchonine sulfate U.S.P. IX, cinchonidine sulfate U.S.P. X, sodium silicate solution (technical, 40–42° Be) were used.

Procedure.—The preparation of our gels was essentially that used by Dickey (6). The desired quantity of alkaloidal salt (sulfate) was dissolved in 130 ml. of 5.7 *N* hydrochloric acid, and this solution was added to 42 Gm. of sodium silicate solution (technical grade) which had been diluted to 200 ml. with distilled water. After standing overnight, the entire solution formed a jelly which was dried under a current of air in a hood. The dried gel was triturated, and the material which passed through a No. 40 sieve was washed with methyl alcohol in a Soxhlet extractor for 48 hours, after which time all the alkaloid had been removed. The absence of any alkaloid could be demonstrated by the lack of rotation of plane polarized light and the lack of precipitation by alkaloidal reagents in samples of the wash liquor. Furthermore, small quantities of the gel were not charred when placed in a Bunsen flame.

The catalysts were prepared by the method of Hartung (9) using 100 mg. of palladous chloride per gram of gel and sodium acetate as a buffer. Hydrogenations were performed in absolute ethanol on a low-pressure Parr hydrogenation apparatus at about 60 p.s.i.g. using 1.0 Gm. of catalyst. Heating was accomplished using an infrared heat lamp.

These catalysts all possessed a low order of activity, requiring about 32 hours for the reduction of 0.05 mole of α-methylcinnamic acid. After 24 hours, an additional 1.0 Gm. of the catalyst was added and the hydrogenation continued for another 8 hours. No kinetic studies were attempted because of the abnormally long reduction period and the lack of an adequate temperature control.

Following hydrogenation, the catalyst was removed by filtration, and the alcohol evaporated at room temperature leaving an oily residue or crystals depending on the extent of reduction. The product was distilled *in vacuo* collecting the fraction boiling from 125–130°/0.5 mm. Hg (uncorrected).[1] The optical rotation was taken in benzene using a 1.0 dm. tube and a Kern Aarau polarimeter. Literature values for the boiling point and the specific rotation of dihydro-α-methylcinnamic acid were 160°/13 mm. Hg and 27.06° (benzene), respectively (10).

RESULTS

Silica gels prepared in the presence of quinine, quinidine, cinchonidine, and cinchonine produced stereospecific catalysts when used as carriers for palladium as shown in Table I. Within experimental error, palladized gels made in the presence of quinine and cinchonidine were twice as effective in producing an optically active product as those prepared using quinidine and cinchonine. Also, no enhancement or lowering of quinine and cinchonidine induced stereoselectivity was observed when equal mixtures by weight of quinine and cinchonidine, cinchonidine and cinchonine, quinine and cinchonine, or quinine and quinidine were used to prepare the gels.

The stereoselectivity of the gels does not appear to decrease significantly with age. So far, our evidence indicates a decrease in catalytic activity by the palladized 6-month-old gel. Further data must be obtained before definite statements can be made

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[1] The product was also identified by its neutralization equivalent.

TABLE I.—RESULTS OF THE HYDROGENATION EXPERIMENTS USING α-METHYLCINNAMIC ACID

Carriers	α-Methyl Cinnamic Acid Concn., %[a]	$[\alpha]_D^{25}$	Optical Yield, %[b]	Over-all Yield, %
QN 0.5 SG[c]	59.9	+0.87	3.21	81.1
QDN 0.5 SG[c]	44.1	+0.45	1.66	68.0
CN 0.5 SG[c]	63.2	+0.47	1.74	77.1
CDN 0.5 SG[c]	64.8	+0.88	3.25	87.9
CDN 0.25-CN 0.25 SG[d]	52.8	+0.86	3.18	70.9
QN 0.25-CN 0.25 SG[d]	57.6	+0.87	3.21	78.1
CDN 0.25-QN 0.25 SG[d]	55.5	+0.86	3.18	67.7
QDN 0.25-QN 0.25 SG[d]	65.5	+0.84	3.10	79.9
Plain SG	49.5	0.00	0.00	44.3
Aged QN SG (6 mo.)	39.5	+0.85	3.14	48.2

[a] Weight in volume in benzene. [b] Per cent optical yield is calculated by

$$\% \text{ optical yield} = \frac{[\alpha]_D^{25} \text{ (exptl.)} \times 100}{[\alpha]_D^{25} \text{ (lit.)}}$$

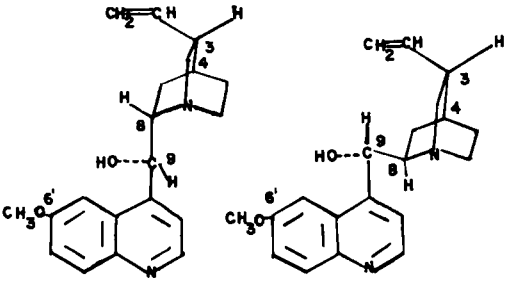
[c] Quinine silica gel which was prepared using 0.5 Gm. of quinine sulfate in the gel preparation. QDN = quinidine sulfate; CN = cinchonine sulfate; CDN = cinchonidine sulfate. [d] Silica gels prepared using mixtures of the individual alkaloids as indicated.

regarding the effects of age on the gel. Experiments are in progress to demonstrate the effects of alkaloid concentration on the stereoselectivity of the gels and will be reported at a later date.

It should be re-emphasized that no alkaloid was present during the hydrogenations of α-methylcinnamic acid, having been removed by the washing procedure. Evidently, the alkaloids have induced a change in the silica gel itself, making it stereoselective. Also, increased catalytic activity was noted in the palladized cinchona-treated gels over the palladized plain gel.

Only dextrorotatory product was obtained no matter which alkaloid was employed in the preparation of the gel. The difference noted was in the respective optical yields of the product. This might be explained by reference to the steric structures of the cinchona alkaloids as determined by Woodward (11) and given in Fig. 1. Note that quinine and quinidine are not antimers but diastereoisomers. They possess opposing configurations about carbon atoms eight and nine, but the configurations about carbons three and four are the same in the two alkaloids. Quinine and quinidine differ from cinchonidine and cinchonine by possessing a methoxy group at position 6′. Configurationally, cinchonidine corresponds with quinine and cinchonine with quinidine.

The experimental data indicate that the asymmetric inductive effects from quinine or cinchonidine might result from a potentiation of the asymmetric induction stemming from carbon atoms three and four by the asymmetric induction from carbons eight and nine. On the other hand, asymmetric induction from carbons eight and nine possibly opposes that from carbons three and four in the asymmetric inductive effects stemming from quinidine and cinchonine.



Quinine Quinidine

Fig. 1.—Steric structures of cinchona alkaloids.

SUMMARY

Stereoselective reduction of α-methylcinnamic acid was accomplished using palladium-on-silica gel catalysts. The silica gels prepared in the presence of cinchona alkaloids all produced dextrorotatory product. When used as carrier for palladium, the gels prepared in the presence of quinine and cinchonidine produced approximately twice the optical yields of (+)-dihydro-α-methylcinnamic acid as those prepared in the presence of quinidine or cinchonine.

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