Hydrogenolysis of Benzyl Esters with Palladium-on-Carbon Catalysts

By HAROLD L. SMITH, EARLE S. BROWN, J. DOYLE SMITH, and JOHN ANDRAKO

Further studies to demonstrate the possibility of substrate and stereospecific sites on palladized charcoal hydrogenation catalysts have been made. The rates of hydrogenation of the benzyl esters of (+), (−), (±), and *meso*-tartaric acids, (±) malic acid, D-, L-, and DL-aspartic acids were measured. The rates were observed to be identical for the benzyl esters of the tartaric acids and the malic acid, indicating the possibility that these five substrates can utilize the same catalytic sites for debenzylation. A hydroxy group and the two carbobenzyloxy groups are postulated as being involved in the catalyst–substrate complex. The dibenzyl aspartates when compared to one another undergo debenzylation at the same rates. The rate of hydrogenolysis of dibenzyl succinate was found to be significantly different when compared to the rates of these other substances. Dibenzyl succinate, being devoid of a hydroxy group or an amino group, would not be expected to utilize the same sites as the dibenzyl esters of tartaric, malic, and aspartic acids.

HARTUNG and co-workers (1) have postulated the existence of substrate and stereospecific sites at the surface of a palladium-on-carbon hydrogenation catalyst. The postulate utilizes the concept due to Ogston (2) of a three-point interaction of a substrate with an enzyme and proposed by him to account for the stereospecificity of enzyme reactions. It is assumed in the postulate, according to Hartung and co-workers, that a three-point attachment of reducible substrate to the active centers in the preliminary adsorption phase of a catalytic hydrogenation also occurs. This requires that three palladium-active centers on the catalytic surface be properly spaced to accommodate the interacting groups of the substrate. Presumably, palladium is deposited at random on the charcoal surface in small clusters of atoms. This means that all possible dimensions between such centers are available down to a minimum distance controlled by the surface topography and the amount of palladium deposited. In Fig. 1, I and II may represent hypothetical enantiomeric sites in which the spacing of the active centers in the two are identical or nearly so, but the active centers are so positioned that they constitute a mirror image pair. Such a pair would be expected to afford a racemic product when jointly acting on a symmetrical substrate. If, however, an unsymmetrical compound were modified on I, then II would not function and vice versa. Sites represented by III and IV in Fig. 1 would accommodate an enantiomeric pair of substrate molecules with dimensions differing from those suitable for I and II.

It should be possible to demonstrate this stereospecificity by utilizing a substrate system composed of the (+), (−), and racemic forms which may be hydrogenated. The (+) and (−) isomers theoretically should show identical hydrogen uptake curves when hydrogenated individually. One should expect this because the random distribution of active centers should lead to equal numbers of enantiomeric sites. Reduction of the racemic modification should show a substantially faster hydrogen uptake than the (+) and (−) isomers. However, one would not expect to observe an exact doubling of the rate since the possibility exists that enantiomeric sites could show an active center in common, *e.g.*, in V of Fig. 1, thus preventing simultaneous operation of these two sites.

The present study was made as an attempt to demonstrate the possibility of substrate and stereospecific sites on palladized charcoal hydrogenation catalysts. The substrates chosen for investigation are the dibenzyl esters of (+), (−), (±), and *meso*-tartaric acids, (±)-malic acid, D-, L-, DL- aspartic acids, and succinic acid. These esters readily undergo hydrogenolysis of the

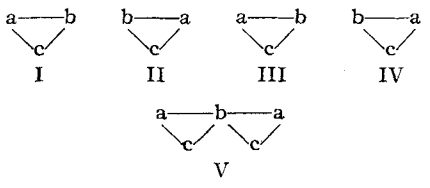


Fig. 1.—Hypothetical active sites on a catalyst surface.

Received July 30, 1964, from the Department of Chemistry and Pharmaceutical Chemistry, School of Pharmacy, Medical College of Virginia, Richmond.
Accepted for publication May 27, 1965.
Presented to the Scientific Section, A.PH.A., New York City meeting, August 1964.
This investigation was supported by grant GM-05895 from the U. S. Department of Health, Education and Welfare, Washington, D. C.

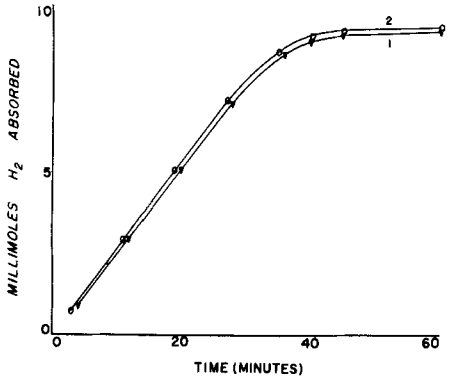


Fig. 2.—Hydrogenolysis of isomeric dibenzyl tartrates, 5.0 mmoles in absolute ethanol with 0.5 Gm. A-25 Pd-on-charcoal catalyst. Key: 1, dibenzyl (−)-tartrate; 2, dibenzyl (+)-tartrate.

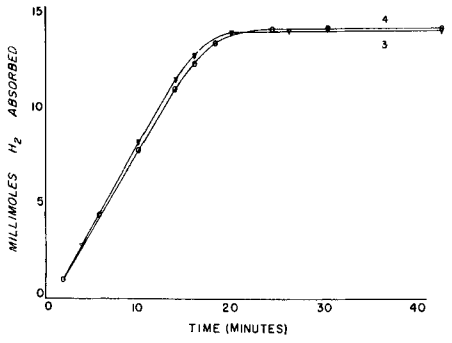


Fig. 3.—Hydrogenolysis of dibenzyl tartrate, 7.5 mmoles in absolute ethanol with 0.5 Gm. A-25 Pd-on-charcoal catalyst. Key: 3, dibenzyl (−)-tartrate; 4, dibenzyl (±)-tartrate.

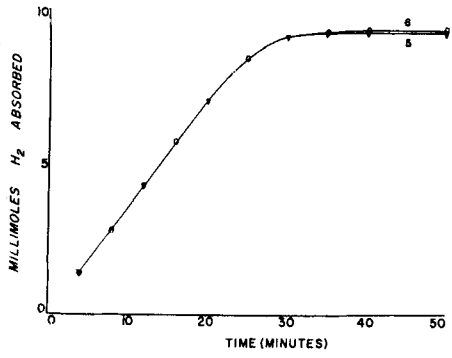


Fig. 4.—Hydrogenolysis of dibenzyl tartrate, 5.0 mmoles in absolute ethanol with 0.5 Gm. A-25 Pd-on-charcoal catalyst. Key: 5, dibenzyl (−)-tartrate; 6, dibenzyl *meso*-tartrate.

benzyl groups in the presence of palladium-on-charcoal catalysts under the conditions used.

The hydrogenation apparatus used in this study was of the type described by Meschke and Hartung (3). Its design permits hydrogenations to be carried out at constant temperature and pressure and with constant stirring.

In each instance where the rates were to be compared, the split catalyst technique which involves the use of portions of the same catalyst was utilized, and the conditions under which the hydrogenations were carried out were duplicated from one run to the next as closely as possible.

Figures 2, 3, and 4 summarize the hydrogenations which were carried out on the various dibenzyl tartrates. In Fig. 5, the rate of hydrogenolysis of (±)-dibenzyl malate is compared with that of dibenzyl *meso*-tartrate. An inspection of these curves shows that all of the substrates undergo hydrogenolysis at essentially the same rate.

Figure 6 summarizes the hydrogenations of the isomeric dibenzyl aspartate *p*-toluenesulfonate salts during approximately the first 20 min. of the

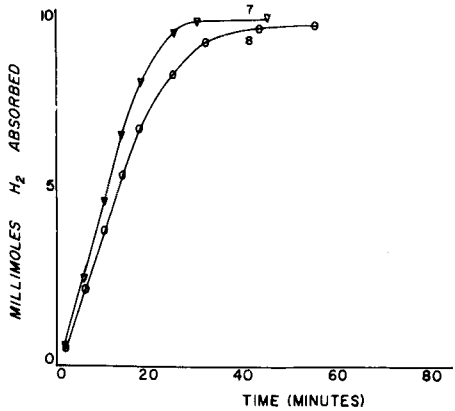


Fig. 5.—Hydrogenolysis of dibenzyl esters, 5.0 mmoles in absolute ethanol with 0.5 Gm. A-25 Pd-on-charcoal catalyst. Key: 7, dibenzyl (−)-tartrate; 8, dibenzyl (±)-malate.

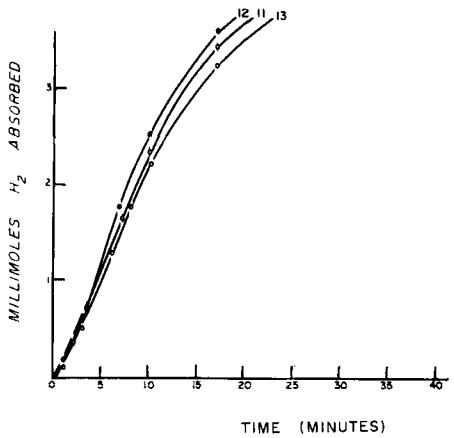


Fig. 6.—Hydrogenolysis of dibenzyl aspartate *p*-toluenesulfonate salts, 1.93 mmoles in absolute ethanol with 0.5 Gm. A-25 Pd-on-charcoal catalyst. Key: 11, dibenzyl D-aspartate; 12, dibenzyl L-aspartate; 13, dibenzyl DL-aspartate.

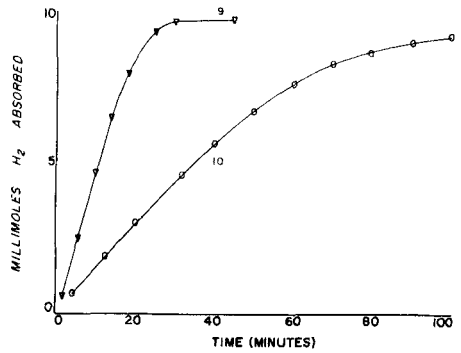


Fig. 7.—Hydrogenolysis of dibenzyl esters, 5.0 mmoles in ethanol with 0.5 Gm. A-25 Pd-on-charcoal catalyst. Key: 9, dibenzyl *meso*-tartrate; 10, dibenzyl succinate.

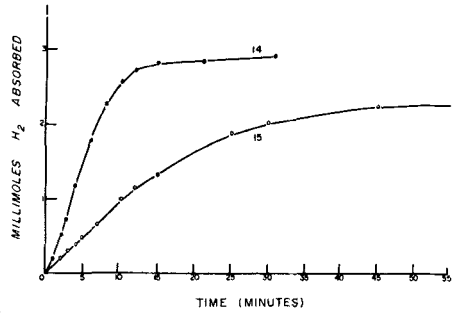


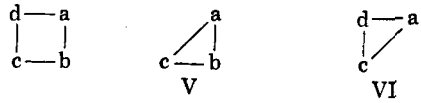
Fig. 8.—Hydrogenolysis of dibenzyl esters, 1.09 mmoles in absolute ethanol with 0.5 Gm. A-25 Pd-on-charcoal catalyst. Key: 14, dibenzyl DL-aspartate; 15, dibenzyl succinate.

reaction. These substrates when compared with one another also show practically identical rates.

Figures 7 and 8 compare the rate of hydrogenolysis of dibenzyl succinate with dibenzyl *meso*-tartrate and racemic dibenzyl aspartate *p*-toluenesulfonate. In each instance the rate at which dibenzyl succinate undergoes hydrogenolysis, curves 10 and 15, is significantly slower.

DISCUSSION OF RESULTS

Although comparison of the rates at which the isomeric dibenzyl tartrates, isomeric dibenzyl aspartate *p*-toluenesulfonate salts, and the racemic dibenzyl malate undergo hydrogenolysis reveals that the racemic forms do not debenzylate at a significantly faster rate, the results may be interpreted by postulating that during the modification of these esters each is attached to the active centers at the surface of the catalyst by three points. Such points of attachment, with regard to the substrate molecules, apparently involve the two carbobenzyloxy groups and a hydroxy group. The four substrate molecules which contain at least one hydroxy group are represented in Fig. 9 in the conformations necessary for substrate interaction with a catalytic surface which is planar or nearly so. If the carbobenzyloxy groups and the hydroxy groups of, *e.g.*, dibenzyl (+)-tartrate are allowed to rest on a planar surface, the four points at which the molecule touches the catalytic surface may be represented as in Scheme I, where a, b, c, and d represent the possible points of attachment at the surface of the catalyst. With the ester in this conformation and using normal bond lengths and bond angles, a calculation revealed that points a, b, c, and d essentially describe a square. Therefore, the active sites which are postulated to be operative for this reduction may be represented as follows:



all sites [(+) or (−)-genic] (mirror image of V)

Inspection of the configurations of the substrates that underwent hydrogenolysis at the same rate reveals that both centers V and VI would be operative during their reductions. It follows, therefore, that these substrates should debenzylate at essentially the same rates. The same interpretation can be applied to account for the similar rates of debenzylation observed with the isomeric dibenzyl aspartate *p*-toluenesulfonates.

Dibenzyl succinate contains neither the proper groups nor the necessary geometry for the reduction

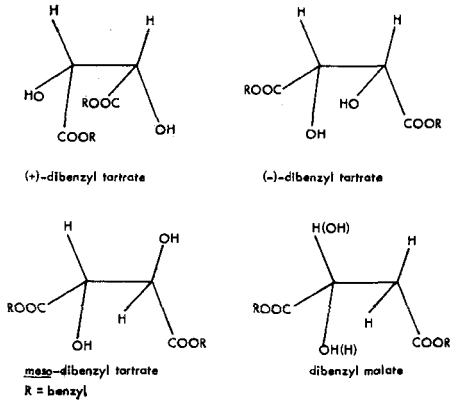
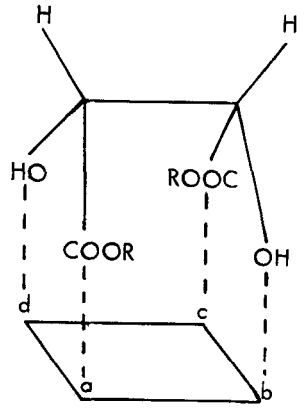


Fig. 9.—Conformations of tartrate and malate esters necessary for attachment to a planar or near planar catalytic surface.



Scheme I

on centers of the type utilized by, *e.g.*, the tartrates, but would require sites of some other dimensions and thus should be debenzylated at a different rate.

SUMMARY

1. The dibenzyl esters of (+), (−), and *meso*-tartaric acids, (±)-malic acid, and of D-, L-, and DL-aspartic acids have been prepared and characterized.

2. The rates of debenzylation of these esters as well as of dibenzyl succinate have been determined and compared.

3. The similar rates of hydrogenation observed for the dibenzyl tartrates, racemic dibenzyl malate, and the isomeric dibenzyl aspartates may be explained by the assumption that these substrates can utilize the same catalytic sites for debenzylation. It is postulated that the two carbobenzyloxy groups and a hydroxy or amino groups, depending on the substrate in question are involved in the catalyst–substrate complex.

EXPERIMENTAL[1]

Dibenzyl (−)-Tartrate.—To a solution of 32.4 Gm. (0.3 mole) of benzyl alcohol in 200 ml. of dry benzene contained in a 500-ml. round-bottom flask fitted through a Dean-Stark trap to a condenser were added 22.5 Gm. (0.152 mole) of (−)-tartaric acid and 0.5 Gm. of sulfosalicylic acid. The mixture was stirred using a magnetic stirrer and was refluxed until 4.4 ml. of water was collected in the trap (5 hr. or more). The reaction mixture was cooled, and 100 ml. of ether was added. The resulting solution was washed successively with equal volumes of water, 10% sodium bicarbonate solution, and finally with water. The washed solution was gently warmed on the steam bath to evaporate most of the solvent. The residue which solidified on cooling was recrystallized twice from carbon tetrachloride and once from methanol–water, yielding 32 Gm. (61%) of crude ester which melted at 52–57°. This ester as well as the other tartrate esters which were prepared formed gels when warmed solutions in various solvents were cooled. For this reason it was difficult to obtain good yields of pure products. The crude ester was dissolved in methanol, 0.5 Gm. of charcoal was added and the mixture was heated gently on the steam bath for 30 min. The charcoal was removed by filtration, and the ester was precipitated from the filtrate while being cooled in an ice bath by the addition of water. After further recrystallization from methanol–water, 6.1 Gm. (12%) of dibenzyl (−)-tartrate melting at 67.5–69° was obtained. $[\alpha]_D^{25} = -12.6°$ (c = 0.3987, ethanol).

Anal.—Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.30; H, 5.89.

Dibenzyl (+)-Tartrate.—The general procedure used for the preparation of the dibenzyl ester of (−)-tartaric acid was used. The dibenzyl (+)-tartrate which was obtained melted at 67–69° [lit. m.p. about 50° (4)] and weighed 5.5 Gm. (11%). $[\alpha]_D^{25} = +12.6°$ (c = 0.3976, ethanol).

Anal.—Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.19; H, 5.40.

Dibenzyl meso-Tartrate.—Seventy-five grams (0.45 mole) of *meso*-tartaric acid monohydrate, 108 Gm. (1 mole) of benzyl alcohol, 0.75 Gm. of *p*-toluenesulfonic acid, and 500 ml. of benzene were used to prepare this ester according to the procedure outlined for dibenzyl (−)-tartrate. After three recrystallizations from benzene, 73.5 Gm. (55%) of product melting at 103.5–105.5° was obtained.

Anal.—Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.30; H, 5.68.

Dibenzyl (±)-Tartrate.—When the racemic ester was needed for the hydrogenation experiments, equimolar amounts of the dibenzyl esters derived from (+) and (−) tartaric acids were used.

Dibenzyl (±)-Malate.—Twenty grams (0.25 mole) of benzyl alcohol, 16.8 Gm. (0.12 mole) of racemic malic acid, 0.25 Gm. of sulfosalicylic acid in 200 ml. of benzene were used to prepare this ester according to the procedure outlined for dibenzyl (−)-tartrate. The dibenzyl malate which was isolated by distillation boiled at 197–205° at 0.14–0.18 mm. Hg.

Anal.—Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.48; H, 5.87.

Dibenzyl DL-Aspartate p-Toluenesulfonate.—The procedure used to prepare this ester is a slight modification of the procedure described by Miller and Waelsch (5) for the preparation of benzenesulfonates of amino acid benzyl esters.

Racemic aspartic acid, 6.65 Gm. (0.05 mole), and *p*-toluenesulfonic acid, 21.8 Gm. (0.12 mole), were mixed with 50 ml. of benzyl alcohol in a round-bottom flask equipped for vacuum distillation. The mixture was heated on the steam bath until solution was effected. The excess benzyl alcohol was distilled off by vacuum distillation at 127°/1.9 mm. The orange-brown viscous residue was poured into an evaporating dish, and 50 ml. of ether was added. On standing overnight a solid product was obtained. The crude product was recrystallized three times from absolute ethanol. The dibenzyl (±)-aspartate *p*-toluenesulfonate obtained weighed 16 Gm. (66%) and melted at 130–133°. [Lit. m.p. about 106° (6).]

Anal.[2]—Calcd. for $C_{25}H_{27}NO_7S$: C, 61.83; H, 5.61; N, 2.88; S, 6.60. Found: C, 62.06; H, 5.67; N, 3.18; S, 6.90.

Dibenzyl L-Aspartate p-Toluenesulfonate.—Prepared as described above, this compound was obtained in 34% yield and melted at 155–157°. [Lit. m.p. 157–158° (7).] $[\alpha]_D^{27} + 22.2$ (c = 1.66, dioxane).

Anal.[2]—Calcd. for $C_{25}H_{27}NO_7S$: C, 61.83; H, 5.61; N, 2.88; S, 6.60. Found: C, 62.07; H, 5.64; N, 3.02; S, 6.83.

Dibenzyl D-Aspartate p-Toluenesulfonate.—Prepared as described above, this compound was obtained in 40% yield and melted at 155–157°. $[\alpha]_D^{27}$ −22.2 (c = 1.66, dioxane).

Anal.[2]—Calcd. for $C_{25}H_{27}NO_7S$: C, 61.83; H, 5.61; N, 2.88; S, 6.60. Found: C, 61.84; H, 5.44; N, 3.08; S, 6.80.

Dibenzyl Succinate.—This compound was obtained from commercial sources and had a melting range of 43–45°. [Lit. m.p. 44–46° (8).]

Catalysts.—The palladium-on-charcoal catalysts were prepared by the method described by Young and co-workers (9). In order to avoid catalyst

[1] Temperatures uncorrected.

[2] Analyses by Weiler and Strauss, Oxford, England.

variability when rates were to be compared, enough catalyst was prepared so that portions of the same catalyst could be used in each of the runs. The catalysts were dried in a vacuum desiccator over P_2O_5 for 24 hr. after which they were pulverized and mixed to insure uniformity and then stored in tightly stoppered bottles until used. The strength of the catalyst used in the various hydrogenations is indicated by, *e.g.*, A-100, in which the A designates that the catalyst was prepared in the presence of sodium acetate, and the number indicates the milligrams of $PdCl_2$ used per gram of charcoal.

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Carbonation of Aqueous Solutions with Acid Anhydrides

Slow Acidification in Homogeneous Systems

By TAKERU HIGUCHI, JOHN PERRIN*, JOSEPH ROBINSON, and ARNOLD J. REPTA

A novel means of achieving a superior degree of carbonation by use of sodium bicarbonate and various latentiated acidifiers is presented. The physical chemical basis of the formulation depends on essentially total dissolution of the bicarbonate salt and the latentiated acidifier prior to formation of any free carbonic acid. Data are presented to show the feasibility of the use of glutaric anhydride as the acid precursor. The pH profile of hydrolysis of the anhydride and its behavior in the presence of nucleophiles such as CO_3^{2-}, HPO_4^{2-}, etc., are discussed. It is shown that a markedly greater degree of supersaturation with respect to carbon dioxide can be achieved by this route than is possible by the conventional method of dissolving sodium bicarbonate and a solid acid in water.

ALTHOUGH chemical carbonation of pharmaceutical and beverage solutions has been practiced for generations, the basic process involving acidification of bicarbonate has changed little despite the fact that present methods suffer from serious theoretical drawbacks. In practice, solid mixtures of sodium bicarbonate and organic acids such as citric and tartaric with other pharmaceutically necessary ingredients are usually added to cold water. In such systems it is practically impossible to achieve much more than an atmospheric saturation of the solution with respect to the released carbon dioxide, the excess gas normally escaping from the solution as rapidly as the ingredients dissolve. The exact geographical site where carbon dioxide is generated depends on the relative dissolution rates of the bicarbonate and the acid particles. If the acid dissolves first, then the bulk of the reaction takes place in the saturated solution in close proximity to the undissolved bicarbonate particles. If the bicarbonate dissolves faster, the reaction takes place essentially near the surface of the undissolved acid. Such suspension systems did not favor supersaturation with respect to carbon dioxide since the particulate solids act as nuclei for bubble formation.

Thus, for the more common case in which we have the reaction

$$[NaHCO_3]_{solid} \rightarrow Na^+ + HCO_3^-$$
$$\swarrow \text{ dissolved acid}$$
$$H_2CO_3 \rightarrow (CO_2)_{aq} \rightarrow CO_2 \text{ (gas)}$$

occurring largely in the vicinity of the undissolved bicarbonate particles, the rate of escape of gaseous carbon dioxide is facilitated by two factors. Since the organic acids are normally present in a substantial excess, localized areas of a high degree of supersaturation with respect to the gas form around each particle of the bi-

Received April 2, 1965, from the School of Pharmacy, University of Wisconsin, Madison.
Accepted for publication June 11, 1965.
Presented to the Scientific Section, A.PH.A., Detroit meeting, March 1965.
This investigation was supported in part by a grant from the American Chicle Co., Warner-Lambert Pharmaceutical Co., Long Island City, N. Y.
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