formyl-7-hydroxy-2-methylchromone (IIIb) from ethyl alcohol, m.p. 202–204° (dec.). Yield was *ca.* 65%.

Anal. Calcd. for $C_{13}H_{10}O_7$: C, 56.11; H, 3.59. Found: C, 55.83; H, 3.76.

(b) *Hydrogen peroxide.* Oxidation of IId with hydrogen peroxide in alkaline medium according to the procedure described for the oxidation of IIa[7] led to the formation of yellowish needles of 4-(ω-carboxymethoxy)-6-hydroxybenzofuran-5-carboxylic acid (Vc), m.p. 229–230° (dec.). It gives a blue color when its alcoholic solution is treated with aqueous ferric chloride solution.

Anal. Calcd. for $C_{11}H_8O_7$: C, 52.38; H, 3.17. Found: C, 52.35; H, 3.58.

Oxidation with hydrogen peroxide in alkaline medium. (a) Ig. One gram of Ig gave upon oxidation with hydrogen peroxide in alkaline medium[7] 4,7-di-(ω-carboxymethoxy)-6-hydroxybenzofuran-5-carboxylic acid (Va) as colorless needles from water (*ca.* 0.5 g.), m.p. 222–223° (dec.). It gives a blue color with ferric chloride.

Anal. Calcd. for $C_{13}H_{10}O_{10}$, H_2O: C, 45.34; H, 3.48. Found: C, 45.42; H, 3.70.

(b) Ik. Similarly, oxidation of 1 g. of Ik with the same reagents under the same experimental conditions, led to the formation of colorless needles from ethyl alcohol (*ca.* 0.6 g.) of 7-(ω-carboxymethoxy)-6-hydroxy-4-methoxybenzofuran-5-carboxylic acid (Vb), m.p. 192–194° (dec.). It gives a blue color with ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_8$: C, 51.06; H, 3.54. Found: C, 51.28; H, 4.18.

(c) Ib. Oxidation of 1 g. of Ib[2] with hydrogen peroxide, as described for Ig, led to the formation of colorless needles from ethyl alcohol of 4-(ω-carboxymethoxy)-6-hydroxy-7-methoxybenzofuran-5-carboxylic acid (Vd) (*ca.* 0.5 g.), m.p. 202–203° (dec.). It gives a blue color with ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_8$: C, 51.06; H, 3.54. Found: C, 51.03; H, 4.18.

Alkaline hydrolysis. (a) Ik. Refluxing 1 g. of Ik with aqueous sodium hydroxide solution (40 ml.; 15%) for 2 hr., followed by cooling the reaction mixture and acidification with cold dilute hydrochloric acid, gave pale-yellow needles from dilute ethyl alcohol of 5-acetyl-7-(ω-carboxymethoxy)-6-hydroxy-4-methoxybenzofuran (IVa) (ca. 0.6 g.), m.p. 171–172°. It gives a green color with ferric chloride.

Anal. Calcd. for $C_{13}H_{12}O_7$: C, 55.71; H, 4.28. Found: C, 55.73; H, 4.61.

(b) IId. Similarly, treatment of 1 g. of IId with sodium hydroxide under the above mentioned conditions led to the formation of canary-yellow needles from ethyl alcohol (*ca.* 0.4 g.) of 5-acetyl-4-(ω-carboxymethoxy)-6-hydroxybenzofuran (IVb), m.p. 217–218° (dec.). It gives a blue color with ferric chloride.

Anal. Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.00. Found: C, 57.51; H, 4.10.

Preparation of 6-Formyl-5-hydroxy-7-methoxy-2-methylchromone (IXc). One half gram of 6-formyl-5,7-dimethoxy-2-methylchromone[7] was refluxed for 1 hr. with a mixture of 10 ml. of concentrated hydrochloric acid and 10 ml. of water. The solid obtained upon cooling the reaction mixture was collected and crystallized from ethyl alcohol as colorless crystals (250 mg.), m.p. 250° (dec.).

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.53; H, 4.27. Found: C, 61.63; H, 4.14.

IXc is insoluble in aqueous sodium hydroxide solution (5%) and acquires a yellow color when treated with 50% sulfuric acid. It gives a violet-red color with ferric chloride.

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Palladium Catalysts. X.[1,2] Substrate-Specific and Stereospecific Centers

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It is postulated that a hydrogenation catalyst prepared by depositing palladium on a suitable carrier consists of centers differing from each other not only in their reactivity toward specific substrates but toward specific stereoisomers of those substrates. Thus, centers effective for the hydrogenation of a given compound differ appreciably from those effective for another compound or even for a stereoisomer. Conditions are outlined for determining the validity of these postulates, and experimental results thus far obtained are in harmony therewith. For example, with identical catalysts the Schiff base formed with benzylamine and a racemic acyloin takes up hydrogen considerably faster than does the Schiff base formed with the D(−)acyloin. Other examples are also given.

Reactions depending on heterogenous catalysis are surface phenomena.[4] Studies of adsorption, reaction kinetics, poisoning, and promoter action lead to the conclusion that the catalytically active surface is nonuniform and that not all areas are equally active.[5]

In previous papers of this series it has been found that for palladium-on-carbon the catalytic properties are influenced by factors such as the presence of other metals,[6] by the ratio of metal to carrier,[7] and by the nature of the anion present when the pal-

(1) For number IX see R. W. Meschke and W. H. Hartung, *J. Org. Chem.* **25**, 137 (1960).

(2) This investigation was supported by Public Health Service Grant RG-5895, National Institutes of Health. For this assistance the authors express grateful appreciation.

(3) Present address: School of Pharmacy, University of South Carolina, Columbia, S. C.

(4) H. S. Taylor and R. M. Burns, *J. Am. Chem. Soc.* **43**, 1284 (1921).

(5) A. B. Kistiakowsky, E. W. Flosdorf, and H. S. Taylor, *J. Am. Chem. Soc.* **49**, 2200 (1927); H. S. Taylor and S. C. Liang, *J. Am. Chem. Soc.*, **69**, 1306, 2989 (1947); R. N. Pease and L. Stewart, *J. Am. Chem. Soc.*, **47**, 1235 (1925); E. B. Maxted *et al.*, *J. Chem. Soc.* **1933**, 502; **1935**, 393; 1938, 1228, 2071; W. W. Russell, *J. Chem. Ed.* **22**, 163 (1945).

(6) W. H. Hartung and Y. T. Chang, *J. Am. Chem. Soc.* **74**, 5927 (1952).

(7) J. G. Young and W. H. Hartung, *J. Org. Chem.* **18**, 1659 (1953).

ladium is deposited;[8] and the kinetics of the reaction may be further modified by the environment in which the reaction proceeds and the product formed.[1,8,9]

These observations coupled with the frequent comparison of heterogeneous catalysis with enzymic processes, especially in view of what is known about the stereochemical pathway of catalytic reactions,[10] raise the question to what extent *in vitro* catalytic processes may be compared with *in vivo* enzymic processes, many of which are known to be highly specific with respect to chemical function and stereo isomers. Thus, in catalysis may there not be a center which is active for one type of compound but quite inert for one of different structure or even configuration? For example, if one expands the "three-point" concept of Ogston[11] (the "multiplet" theory[12] though a bit more complex, may be equally satisfactorily adapted), then the hypothetically different sites in a catalyst may be represented as in Fig. 1.

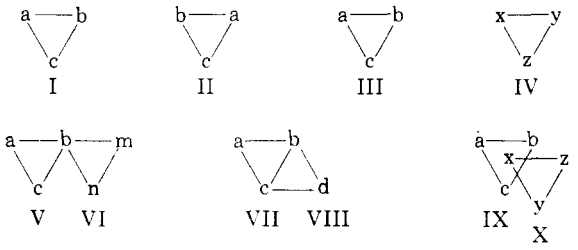

Fig. 1. Hypothetical active sites on a catalyst surface

I is the mirror image of II, randomly present in equal numbers and acting on a symmetrical substrate, e.g. α-oximino propiophenone,[13] jointly afford racemic norephedrine. With an unsymmetrical substate however, for example, the Schiff base resulting from the reaction of methylamine with D(−)acetylphenyl-carbinol, an intermediate which is reduced to natural ephedrine according to the procedure of Hildebrandt and Klavehn,[14] only one of the pair of sites will function. This results in the formation of an optically pure product, while the other enantiomorphous site will be inoperative. III will hypothetically be active for a substrate bearing the same functional groups as the I-specific substrate but with different molecular dimensions. IV is the active site for a different type of compound. V is identical with I, but with point *b* also shared by VI, will be inactive when VI is functioning; that is, V and VI, each active for its respective substrate, cannot function simultaneously. A similar condition exists for the VII-VIII Siamese twin pair and in the IX-X complex where one site is intertwined with another.

The validity of these postulates may be tested by properly designed experiments. It is expected that for a given substrate A only sites I, for example, are functional; all the others are nonfunctional. A properly designed catalyst for modifying optically active A must then have substantially only I sites operating fully throughout the experiment. In the same catalyst another substrate B will be affected by another center, for example IV; with only B present IV alone will be active and all IV-type sites will be working to full capacity. For each of these two cases it is possible to measure the rate at which hydrogen is taken up. If, now, both substrates A and B are present, then the I-site will reduce A at the rate already measured and the IV-site will reduce B; thus the uptake of hydrogen under ideal conditions will be additive. However, since there is no way of knowing what proportion of the V-VI, VII-VIII, and IX-X centers there may be, the rate probably will not be ideally additive, but it should be faster than the rate for either A or B alone.

One may also expect some sites to be highly specific and others less so. Perhaps here is an analogy of cholinesterase as compared to pseudocholinesterase; the former is specific for acetylcholine and the other is more general for the hydrolysis of esters.

Further, if these concepts are valid, then perhaps the chemist may aspire to the preparation of stereospecific catalysts, for example, a catalyst with I-type arrangement without the presence of the enantiomorphous II-type. This is not an idle hope, for already Akabori,[15] by depositing palladium on silk or acetylated silk fibroin, obtained a catalyst which reduces 4-benzyl-2-methyloxazol-5-one to phenylalanine with $[\alpha]_D$ 23.2°.

Few of the readily available compounds lend themselves for experimental examination of the validity of these proposals. However, the results thus far observed and reported here are in harmony with the postulates and sufficiently encouraging to warrant further studies; for these it will be necessary to synthesize substrate reagents that are not readily available.

Kinetic studies were made of available compounds which may be hydrogenated at comparable rates. These were measured according to the procedure described by Meschke.[1] The data are given graphically and are compared in Figs. 2-6.

Fig. 2 deals with the first twenty minutes of the reduction of five millimoles each of fumaric acid

(8) W. D. Cash, F. T. Semeniuk, and W. H. Hartung, *J. Org. Chem.* **21**, 999 (1956).

(9) Z. Csuros, *Muegyetemi Kozlemenyek* **1947**, 110; *Chem. Abstr.* **42**, 3726 (1948).

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(11) A. G. Ogston, *Nature* **162**, 963 (1948).

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(13) Y. T. Chang and W. H. Hartung, *J. Am. Chem. Soc.* **75**, 89 (1953).

(14) G. Hildebrandt and W. Klavehn, U.S. Patent **1,956,950**, May 1, 1934; *Chem. Abstr.*, **28**, 4072 (1934).

(15) S. Akabori *et al.*, *Nature*, **178**, 323 (1956). *J. Chem. Soc. Japan* **77**, 1374 (1956); **78**, 886 (1957) *Biochemistry* (English translation from Russian) **22**, 147 (1957).

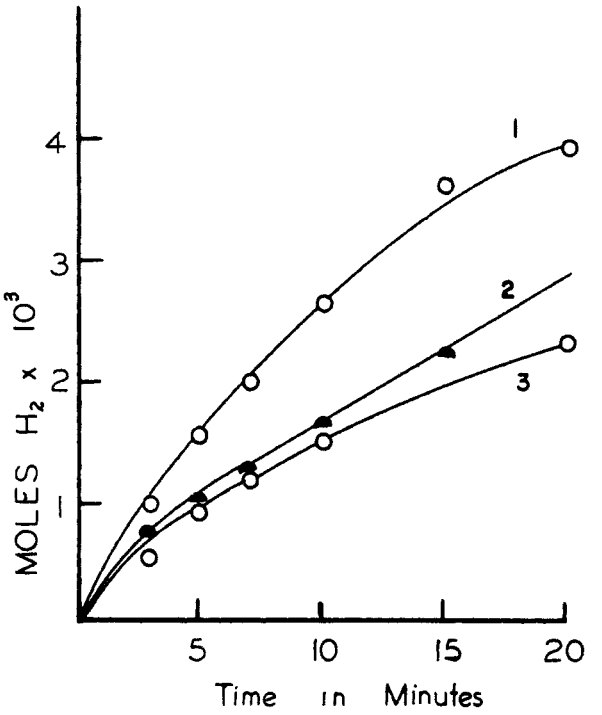

Fig. 2. Reduction of benzyl acetate and of fumaric acid, 5 millimoles in ethanol with 0.5 g. of A-12.5 catalyst. Curve 1, 2.5 millimoles benzyl acetate and 2.5 millimoles fumaric acid. Curve 2, 5 millimoles of fumaric acid. Curve 3, 5 millimoles of benzyl acetate

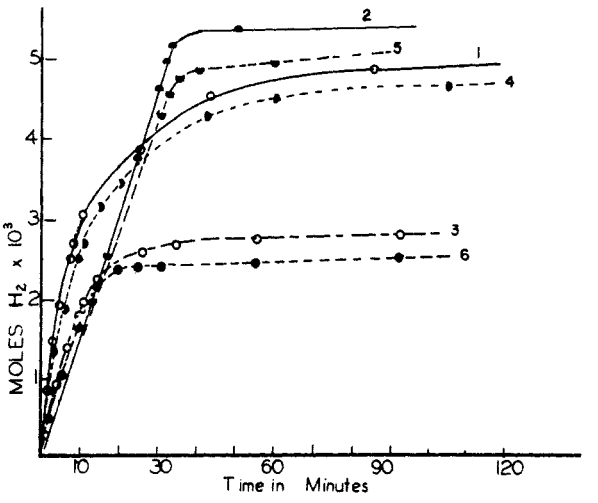

Fig. 3. Reduction of benzyl acetate and fumaric acid, 5 millimoles in ethanol with 0.5 g. of A-12.5 catalyst. Curves 1 and 4, 2.5 millimoles benzyl acetate and 2.5 millimoles fumaric acid. Curves 2 and 5, 5.0 millimoles of fumaric acid. Curves 3 and 6, 5.0 millimoles of benzyl acetate

and the hydrogenolysis of benzyl acetate. For this period of time, the two rates are quite comparable. Curve 1 shows the rate of hydrogen uptake with two and one half millimoles of fumaric acid and two and one half millimoles of benzyl acetate. It will be noted that this is significantly faster, although not additive, than the rates for the two substrates separately. In Fig. 3, curves 1, 2, and 3 are identical

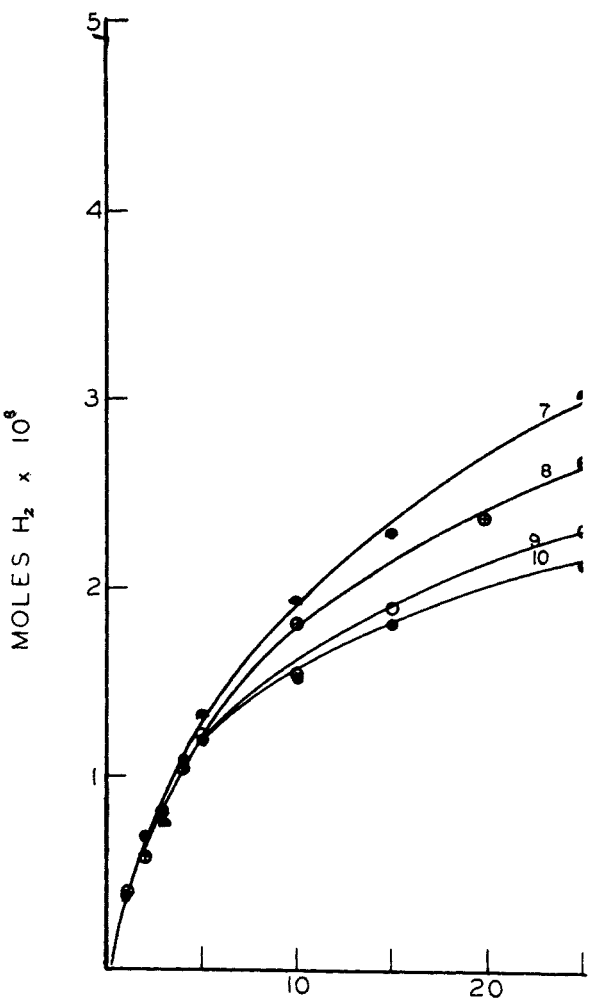

Fig. 4. Reduction of 4-methyl-2-pentene, 5 millimoles in ethanol with 0.5 g. of A-12.5 catalyst. Curve 10, 5 millimoles of *cis* isomer. Curve 9, 5 millimoles of *trans* isomer. Curve 7 and 8, 2.5 millimoles of *cis* isomer and 2.5 millimoles of *trans* isomer

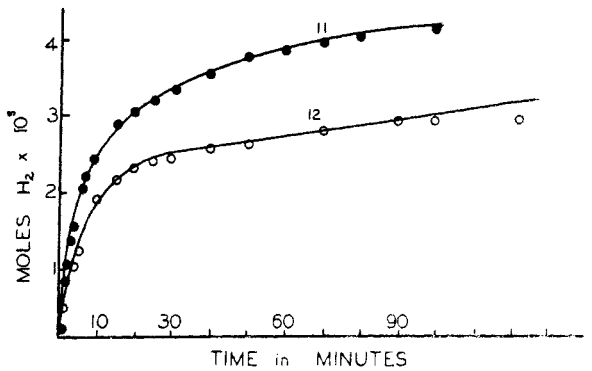

Fig. 5. Reduction of Schiff base from benzylamine and *m*-hydroxyphenylacetylcarbinol, 5 millimoles in ethanol with 0.5 g. of A-100 catalyst. Curve 11, schiff base from racemic acyloin. Curve 12, Schiff base from D-(−)-acyloin

with those of Fig. 2. Fig. 3 also gives curves for typical duplicates to show that the data are quite reproducible. These experiments have been repeated many times with the same results, thus giving them validity.

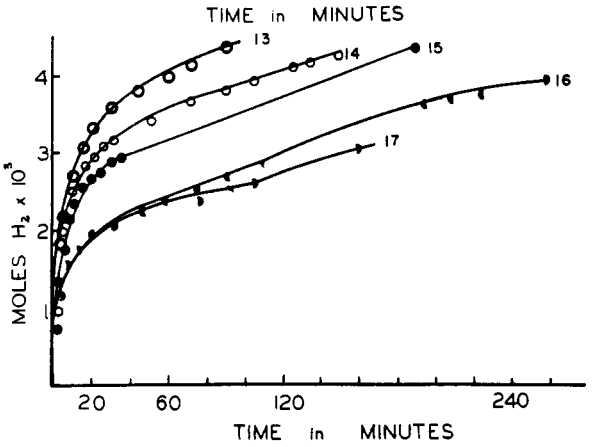

Fig. 6. Reduction of Schiff base from benzylamine and *m*-hydroxyphenylacetylcarbinol in ethanol. Curve 13, Schiff base from d(−)-acyloin with 1 g. of A-100 catalyst. Curves 14 and 15, Schiff base from racemic acyloin with 0.5 g. of A-100 catalyst. Curves 16 and 17, Schiff base from d(−)-acyloin with 0.5 g. A-100 catalyst

Fig. 4 summarizes the reduction of isomeric 4-methyl-2-pentenes during the first 25 minutes of the reaction. It is seen that both the *cis* and the *trans* isomers, curves 10 and 9, respectively, take up hydrogen at a slower rate than an equimolar mixture of the two, curves 7 and 8.

Hydrogenation of fumaric and maleic acids shows practically identical rates of reduction. A mixture of the two proceeds somewhat faster, but since a "minimal" catalyst was not employed, not much reliance can yet be placed on these differences.

The most interesting results are seen with the Schiff base formed from benzylamine and *m*-hydroxyphenylacetylcarbinol, Figs. 5 and 6. Reaction 12, using the substrate prepared from the D-(−)-acyloin is very much slower than reaction II with the racemic substrate. These experiments have been repeated and all results are in agreement with the observations recorded here. Fig. 6 shows more of these. Reaction 14, with racemic substrate, approaches the rate of 13.

DISCUSSION OF RESULTS

Rates of hydrogenation show that (a) the Schiff base of the racemic acyloin is reduced faster than the Schiff base of the D-(−)-acyloin under identical conditions; (b) the Schiff base of the D-(−)-acyloin requires almost twice the quantity of catalyst to be reduced at the same rate as does the racemate; (c) a mixture of equimolar amounts of benzyl acetate and fumaric acid, two chemically unrelated substrates, reduced at a significantly faster rate than either of the individual components by itself. These results are in harmony with the postulate that each substrate has an affinity for a particular site on the catalytic surface and that these sites may be different for specific compounds and specific isomers. The experimental data are not considered adequate to establish conclusively the presence of such stereospecific and substrate-specific centers in the catalyst. Missing are the data, for example in Figs. 5 and 6, for the reduction of the Schiff base of the unavailable L-(+)-acyloin, which would be expected to give curves identical to 12, 16, and 17. Nevertheless, the results thus far obtained are encouraging and further work is in progress, which it is hoped will confirm the hypotheses which prompted these studies.

EXPERIMENTAL

Materials and reagents. The isomeric 4-methyl-2-pentenes were purchased from Phillips Petroleum Company, Bartlesville, Okla. The *cis* isomer boils at 133.2° F. and the *trans* isomer boils at 137.1°F.

D-(−)-*m*-Hydroxyphenylacetylcarbinol was graciously supplied by Messrs. J. M. Sprague and E. L. Engelhardt of Merck Sharp and Dohme, West Point, Pa. After crystallization from ethyl acetate and hexane, it melted at 126–127°, $[\alpha]$, −341.7° in water; these values agree with those previously reported.[16] It was racemized according to the directions of Engelhardt, crystallized from ethyl acetate and hexane and melted at 98–101°. The infrared spectra of the racemic and of the D-(−)-acyloin are indistinguishable, thus confirming that only racemization occurred without concurrent isomerization to *m*-hydroxybenzoylmethylcarbinol.

Benzyl acetate was synthesized according to established procedures.[17]

Fumaric acid, prepared by students, was recrystallized from ethanol, m.p. 194–195° (uncorr.) Maleic acid, also a student preparation, after recrystallization from water, melted 131–132° (uncorr.).

The palladium was generously supplied as pure palladium chloride by Engelhard Industries, Inc., Newark, N. J.

The benzylamine used, Eastman (practical grade), was distilled through a column, the fraction boiling at 81–82°/25 mm. being collected.

Hydrogenation experiments. The preparation of the catalysts is described in earlier papers of this series. The apparatus for making kinetic studies was constructed as described by Meschke.[1]

The products formed by the hydrogenations described are well known except for those formed by the reduction of the Schiff base formed from the *m*-hydroxyphenylacetylcarbinol and benzylamine, *viz.*, m-$HOC_6H_4CHOHC(CH_3)$—$NHCH_2C_6H_5$; the product from the D-(−)-acyloin was isolated as the hydrochloride, $C_{16}H_{19}NO_2HCl$, no definite melting point; Calcd. N, 4.78%; Found, 4.83%. The product from the racemic intermediate was hygroscopic and could not be properly purified for analysis.

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(16) E. L. Engelhardt, private communication.

(17) W. J. Hickenbottom, *The Reactions of Organic Compounds*, Longmans, Green, New York, 1948, p. 416.