The Asymmetric Reduction of β-Methylcinnamic Acid by d-Glucose in the Presence of Raney Nickel

BY T. D. STEWART AND DAVID LIPKIN

The reduction of β-methylcinnamic acid by d-glucose in alkaline solution[1] offers the possibility that the β-phenylbutyric acid produced is optically active. Using Raney nickel as a catalyst, and carefully controlled conditions, we have found the specific rotation of the product to be reproducible and to vary from $[\alpha]^{25}_{5461}$ +0.31° to −0.42° (benzene). The highest specific rotation observed for β-phenylbutyric acid is given by H. Rupe for D light, from which we estimate[2] the specific rotation of the pure *levo* form to be $[\alpha]^{20}_{5461}$ −68.5° (benzene). The present paper concerns itself with the factors producing these small but significant changes in the degree of asymmetric synthesis.

A summary of the results obtained and the experimental conditions is given in Table I. The table headings indicate the initial concentrations of the reactants and the order in which they were added. Columns 2, 3, and 4 give, respectively, the amount of Raney nickel used, expressed in grams per liter of reacting solution, and the time and temperature employed in its preparation from the nickel–aluminum alloy. The temperature specified is that of the oil-bath used for the digestion of the alloy with sodium hydroxide; the catalysts are correspondingly called "hot" or "cold," in reference to this temperature. The relative rates of reaction are shown in column 5, and the specific rotation of the product given in column 6.

Reproducibility of the results is shown in Expts. 16, 24, and 26. A plot of the alkali consumed *vs.* time in these experiments showed absolute consistency of reaction rate. Polarimeter readings were accurate to 0.01° and the specific rotation is accurate to 0.03–0.04°. Experiments 2 and 17 differed in catalyst preparation, and to a minor extent in reagent concentrations.

Amount of Catalyst.—In Fig. 1 are plotted the data for two series of runs, Expts. 12, 8, 9,

(1) Delépine and Horeau, *Compt. rend.*, **204**, 1605 (1937); *Bull. soc. chim.*, [5] **4**, 1524 (1937).

(2) H. Rupe, *Ann.*, **369**, 323 (1909), gives $[\alpha]^{20}$D −57.23° (benzene) as determined by resolution through the menthyl ester. Levene and Marker, *J. Biol. Chem.*, **93**, 761 (1931); **100**, 685 (1933), obtained $[\alpha]^{25}$D −46.8° (benzene) from the cinchonidine salt. After laborious crystallization of the quinine salt we have obtained a sample of acid of $[\alpha]^{25}$D −47.92 and $[\alpha]^{25}_{5461}$ −45.40° (benzene, 0.3280 g./10 ml.).

TABLE I

EXPERIMENTAL CONDITIONS AND RESULTS

Part A. Concentration and order of mixing: β-methyl-cinnamate 0.220 *M*; potassium hydroxide 0.330 *M*; d-glucose 0.440 *M*; nickel. Temperature of reaction 25°C.

Expt.	Catalyst amt. (g./l.)	Prep. and amt. Time, hr.	Prep. and amt. Temp., °C.	Reaction time for 75% completion	Specific rotation $[\alpha]^{20}_{5461}$
12	15	2	118	16 hr.	+0.02
8	30	2	118	2.3	− .35
9	60	2	118	0.7	− .39
18	5	72	20	5.0	− .27
16	10	50	20	1.2	− .30
24	10	72	20	1.0	− .25
26	10	72	20	1.0	− .25
13	30	122	20	0.4	− .09
21	60	72	20	.12	− .04
7	30	4	118	2.6	− .23
6	30	7	118	3.0	− .03

Part B. Same as Part A except temperature of reaction 0°; see Expt. 13.

23	30	72	20	2.3	−0.03

Part C. Concentration same as Part A; order of mixing: salt, alkali, nickel, glucose. See Expts. 8 and 6. Temperature, 25°

20	30	2	118	1.5	−0.13
22	30	7	118	2.3	− .25

Part D. Concentration and order of mixing: β-methyl-cinnamate 0.110 *M*; potassium hydroxide 0.137 *M*; d-glucose 0.165 *M*; nickel. Temperature 25°

15	15	2	118	2.4(62%)	−0.19
28	15	4	118	2.8(62%)	− .11
17	15	7	118	4.9(62%)	+ .12
2	15	7	>118	6.5(62%)	+ .31

Part E. Concentrations one-half those of Part A, except that glucose was 0.165 *M* in Expt. 14. Temperature 25°

14	30	2	118	1.4	−0.32
11	30	2	118	1.1	− .42

and Expts. 18, 24, 13, 21, in each of which the amount of identically prepared catalyst is varied. In the first series the "hot" catalyst was employed; in the second, the "cold" catalyst. It appears anomalous that increased amount of a given surface catalyst should alter the course of the reaction.[3]

(3) It is obviously possible as Wieland, *Ber.*, **46**, 3327 (1913), pointed out, that catalytic dehydrogenation of an alcohol may be followed by catalytic hydrogenation of an acceptor of the hydrogen, and in the present case this could result in a symmetric rather than asymmetric reduction. The effects studied here are conceivably concerned with only a small fraction of the total reaction, or may represent the balance between two concurrent stereochemical processes.
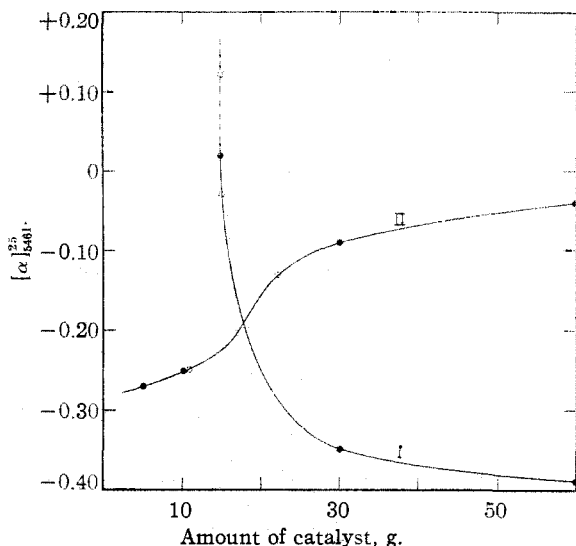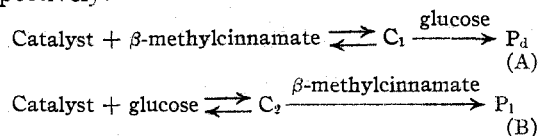
Fig. 1.—Curve I, data from Expts. 12, 8, 9; Curve II, data from Expts. 18, 24, 13, 21. Broken circles plot the specificity only found in Expts. 17, 6 (curve I) and Expts. 20, 22 (curve II), indicative of relative amount of effective catalyst present.

In an attempt to see whether actual concentrations rather than relative concentrations of the reactants were important, all concentrations (and amounts of catalyst) were halved (Expts. 9 and 11) without affecting the specificity appreciably. In all the experiments the ratio of catalyst to reactants increases during the reaction, and the ratio of reactants to each other changes; we are here concerned only with the integrated effect as measured.

A tentative explanation of the effect described in Fig. 1 is as follows. Consider two processes leading to dextro and levo products, P_d and P_l, respectively.

$$\text{Catalyst} + \beta\text{-methylcinnamate} \rightleftharpoons C_1 \xrightarrow{\text{glucose}} P_d \quad \text{(A)}$$

$$\text{Catalyst} + \text{glucose} \rightleftharpoons C_2 \xrightarrow{\beta\text{-methylcinnamate}} P_l \quad \text{(B)}$$

where C_1 and C_2 are reversibly adsorbed molecules. The ratio of the two products will depend upon the equilibrium or steady state values of C_1 and C_2 and the specific rates of the follow reactions. If the two adsorption processes are of such different rates compared to each other or to the rates of the respective follow reactions that the times required for the achievement of equilibrium or steady state values of C_1 and C_2 differ, then the time required for the over-all reaction becomes important. This is so because if the reaction time is short (large amount of catalyst)

the reaction could be complete before the steady states are reached; but if the reaction time is long (small amounts of catalyst) both steady states could be established, leading to a different proportion of the two processes. A seeming independence of the specificity with amount of catalyst at high and low amounts displayed in Fig. 1 could be explained on this basis. The data cannot be used to make a rigid test of this hypothesis, partly because of the factor[3] mentioned above which obscures many effects such as induction periods and absolute rates of reaction, but there are some confirming facts yet to be mentioned. The two curves of Fig. 1, on this basis, suggest that the catalyst will differ in its relative rates of adsorption for the two reactants depending upon the mode of preparation. Thus the "hot" catalyst will be considered provisionally to adsorb glucose the more rapidly (process B) while the "cold" catalyst adsorbs cinnamate the more rapidly. There is no evidence that the "cold" catalyst produces a dextro product (process A) and it may lead only to a levo product when used in small amount and to a racemic product in large amount. On the other hand, the "hot" catalyst apparently participates in both processes.

Time of Catalyst Digestion.—In two series, Expts. 6, 7, 8, and Expts. 17, 28, 15, the nickel alloy was digested for periods of two, four, and seven hours. Concentrations of reactants differed in the two series but were constant within each series. In both cases the negative specific rotations of the products decrease linearly with the digestion time; in the second series this decrease actually results in a positive specific rotation (Expt. 17). This result can be correlated with the facts of the previous section through the simple assumption that continued digestion results in a sintering process that in effect reduces the amount of the catalyst. The destruction of the catalyst may be estimated, for Expts. 6 and 7, from Fig. 1, as amounting to about 50% and 30%, respectively.

Order of Mixing.—In two pairs of identical experiments the order of addition of the glucose and nickel was reversed. In one pair, Expts. 8 and 20, the addition of the sugar last produced a faster reaction and lower specificity in the reaction; in the other pair, Expts. 6 and 22, that order produced a slightly faster reaction but higher specificity (see Fig. 1). In fact, the changes in

specificity were identical in degree, 0.22°, but different in sign.

This behavior may be explained by assuming that the "hot" catalyst, through prior exposure to the β-methylcinnamate, subsequently behaves as would a catalyst which adsorbs that reagent the faster, i. e., a "cold" catalyst. Accordingly in Fig. 1 the specific activities of the products obtained from Expts. 20 and 22 are plotted on Curve II, Fig. 1, and from this the apparent amounts of catalyst present may be read from the plot as 22 g. and 11 g., respectively. As a two-hour "hot" catalyst, the former was 30 g. (Curve I, Fig. 1), or an apparent decrease of 27% effected through change in order of addition of reagents. The latter (Expt. 22) as a seven-hour "hot" catalyst was estimated in the previous section to correspond to only 15.5 g. of two-hour "hot" catalyst, and through the same change in order has decreased 29% (15.5 g. to 11 g.).

Further evidence of the essential identity, aside from effective amount, of the two-hour and seven-hour catalysts, is to be found in the two pairs of experiments, Expts. 8, 15 and 6, 17. In each pair ratios of reactants and catalysts have been similarly changed, in one case with a change in specificity of +0.16° and in the other of +0.15°. This change has been produced by a decrease in the relative glucose concentration and an increase in the dilution (compare the identity of results in Expts. 9, 11), and is in the direction to be expected by a retardation in the rate of adsorption of glucose. A similar effect of decreasing initial glucose concentration is found in Expts. 11, 14.

Effect of Temperature.—Expts. 13 and 23 were identical except for the reaction temperatures, which were 25 and 0°, respectively. The observed decrease in specificity with lower temperature would be expected on the above considerations, because for this catalyst cinnamate is adsorbed the more rapidly, implying that glucose adsorption has a higher activation energy and therefore cinnamate adsorption would be even more highly favored at the lower temperature.

Effect of Platinum Oxide Catalyst.—The use of Adams platinum oxide as catalyst, instead of Raney nickel, results in evolution of some hydrogen gas (dehydrogenation of the sugar) and production of an acid, but virtually no reduction of the cinnamate ion. Different amounts of catalyst were used in two experiments; the order of addition was the same as in Part A, Table I.

Reduction by Means of Monohydric Secondary Alcohols.—d-Hexanol-2 and l-menthol in the presence of alkali and Raney nickel reduced the unsaturated acid as readily as did glucose, but the reduction product was completely racemic. The catalyst used was digested for seventy-two hours at 20° and was not varied in amount. The reaction time was of the same order as in the case of glucose. With menthol, the solvent used was 65% dioxane in water.

It is possible that any one or all of the alcohol groups in glucose are responsible for the reduction of the β-methylcinnamate ion; in fact, it seems plausible that oxidation of the glucose proceeds first to the osone and then, through an internal Cannizzaro reaction, to gluconate ion. We have ascertained by trial that this last step is rapid compared to the rate of the β-methylcinnamate reduction.

All of the experiments performed under carefully controlled conditions are reported. In addition to these, trials using galactose and lactose were made under conditions which with glucose gave a large negative rotation. These sugars gave products with small positive rotations.

Comparison with Enzyme Reactions.—It should be noted that similar variations in enzyme stereo-specificity have been observed in which the same variables of amount of enzyme, order of mixing, etc., have influenced the optical activity of the product of the enzyme reaction even to an inversion of sign. These studies can only be referred to.[4]

Experimental Part

Materials.—The preparation of β-methylcinnamic acid has been described.[5] The potassium hydroxide solution and water used for dilution were carbonate-free. The d-glucose was Baker c. p. analyzed material. For the d-hexanol we are indebted to Mr. J. K. Holmes. It was resolved by Pickard and Kenyon's method[6] and had a rotation $[\alpha]^{18}D$ +11.68° (homogeneous). l-Menthol from McKesson and Robbins, $[\alpha]^{23}_{5461}$ −58.9° (95% alcohol), was used.

The preparation of Raney nickel was carried out in two ways. The desired amount of 20% sodium hydroxide was

(4) (a) Rosenthaler, Biochem. Z., 14, 238 (1908); (b) Krieble and Wieland, THIS JOURNAL, 43, 164 (1921); (c) Krieble, ibid., 35, 1643 (1913); (d) Dakin and Dudley, J. Biol. Chem., 14, 155 (1913); 14, 423 (1913); (e) Neuberg, Biochem. Z., 49, 502 (1913); 51, 484 (1913); Neuberg and Simon, ibid., 186, 331 (1927); 200, 468 (1928); (f) Mayer, Biochem. Z., 174, 420 (1926); Gorr and Perlman, ibid., 174, 433 (1926); Binder-Kotroba, ibid., 174, 443 (1926); R. Kuhn and Heckscher, Z. physiol. Chem., 160, 150 (1926); Widmann, Biochem. Z., 216, 475 (1929).

(5) Lipkin and Stewart, THIS JOURNAL, 61, 3295 (1939).

(6) Pickard and Kenyon, J. Chem. Soc., 99, 49 (1911).

placed in a round-bottomed flask and then at room temperature the 50% nickel–50% aluminum alloy was added as rapidly as foaming permitted (one-half to one hour). The alloy was weighed to yield a given amount of nickel upon the assumption of complete removal of the 50% of aluminum. Actually it was found that the aluminum is not completely removed. After completing the addition of the alloy to the alkaline solution, the flask was placed in a glycerol-bath and heated at 115–120° for the desired time interval, after which it was cooled and the nickel washed by decantation an additional five times after the washings first became neutral to litmus. The second procedure differed in that the alloy was added while cooling the alkali in an ice-bath. The flask was then closed with a Bunsen valve and allowed to stand at room temperature for seventy-two hours with occasional shaking. The catalyst was always prepared just prior to use.

Procedure.—The weighed sample of β-methylcinnamic acid was placed in a volumetric flask and known amounts of potassium hydroxide solution added. When the thermostat temperature was reached, the glucose and catalyst, in either order, were added and the flask filled to the mark and shaken. Zero time was taken when the fourth component was added. The reaction mixture was transferred to a specially designed flask to permit vigorous continuous shaking in the thermostat, with provision for sweeping out the air with pure nitrogen and the taking of periodic samples for titration for alkali concentration. The initial alkali concentration was calculated from the amount of acid and base added; completion and rate of the reaction were indicated by the alkali used up.

After completion of the reaction the nickel was filtered off and discarded and the filtrate acidified and extracted with benzene. The benzene layer, after water washing, was filtered through filter paper moistened with benzene, evaporated to constant weight and the residue taken up in 25 ml. of dry benzene for polarimetric observation and titration. To remove any unreduced β-methylcinnamic acid, the benzene solution was extracted by 50 ml. of 0.5 N

sodium hydroxide and the alkaline extract neutralized to phenolphthalein. Known amounts of 0.020 M potassium permanganate were then added until a small addition gave a color persisting for fifteen minutes; 10 ml. of 1 N sodium hydroxide was then added and a benzene extraction made to remove any acetophenone; after this the solution was acidified and the reduced acid recovered as before. In all but three experiments the unreduced acid present, as shown by the permanganate reaction, amounted to less than 0.3%. In these cases the following amounts were present: Expt. 12, 28%; Expt. 17, 15%; Expt. 18, 17%. The rotations reported are for the permanganate-treated acid, although in most cases the activity of the treated and untreated samples was identical within experimental error. Vacuum distillation of one sample did not change the rotation; vacuum distillation of 35 g. of accumulated samples resulted in a product which crystallized on standing, b. p. (10 mm.) 150–156°, uncorr.; yield 34 g.

Summary

The reduction of β-methylcinnamate ion by d-glucose in alkaline solution, catalyzed by Raney nickel, has been studied with variations in amount of catalyst, temperature, order of mixing, method of preparation of the catalyst, and relative concentrations of solutes. The optical activity in benzene of the resulting β-phenylbutyric acid varied from $[\alpha]_{5461}$ +0.31° to −0.42°, corresponding to about 0.5% asymmetric synthesis. The specificity changed with each variable and a tentative explanation of all of the variations has been presented based upon a simple hypothesis of relative rates of adsorption. Attention is called to the analogous behavior of enzyme catalyzed reactions.

The Redistribution Reaction. IV. Interchange between Triethyllead Chloride and Radioactive Tetraethyllead

BY GEORGE CALINGAERT, HAROLD A. BEATTY AND LEWIS HESS

In the preceding papers of this series[1] it was shown that R_4Pb compounds in general undergo the redistribution reaction in which the intermolecular interchange of R groups leads to the formation of random equilibrium mixtures. Among the effective catalysts for this reaction are the R_3PbX salts, where X is Cl, Br, or I. It is obviously of interest to determine whether these R_3PbX salts also enter directly into this reaction,

and whether both the R and X groups are capable of being interchanged with each other. In the first paper of this series it was indicated that such is the case; the present paper gives the experimental details of the study of the simplest possible reaction of this type, that between R_4Pb and R_3PbX, where all the R groups are identical and no new compounds can be formed; a subsequent paper will describe the more general examples wherein compounds containing different R groups are used.

(1) Calingaert and Beatty, THIS JOURNAL, 61, 2748 (1939); Calingaert, Beatty and Neal, ibid., 2755; Calingaert and Soroos, ibid., 2758.