[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF OAK RIDGE NATIONAL LABORATORY]

Isotope Effects during Catalytic Hydrogenations[1]

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Isotope effects during the heterogeneous catalytic reductions of labeled olefin and carbonyl groups are reported. Stilbene-α-C^{14} is reduced to bibenzyl-α-C^{14} with a 2% isotope effect using Raney Ni in benzene or Pt in ethanol. Acetophenone-α-C^{14} is reduced to 1-phenylethanol-1-C^{14} with an 11.5% isotope effect using Pt in ethanol, and with an 8% isotope effect using lithium aluminum hydride in ether. No exchange of hydrogen between stilbene-α-C^{14} and bibenzyl or between acetophenone-α-C^{14} and 1-phenylethanol or ethanol was observed under the conditions of catalytic reduction employed.

Our recent unanticipated encounter[2] of an isotope effect during the oxidative degradation of 2-phenyl-1-acenaphthenol-1-C^{14} to 8-benzoyl-1-naphthoic-*carboxy*-C^{14} acid emphasized the importance of determining which reactions, commonly used in chemical degradations, might occur with attendant isotopic fractionation, thus possibly leading to erroneous conclusions. To this end an isotope effect during ozonization has recently been reported,[3] and the present paper records the results of isotopic fractionation experiments conducted during several types of hydrogenation processes, both catalytic and chemical. Stilbene-α-C^{14} has been catalytically reduced with two types of catalyst, and acetophenone-α-C^{14} has been reduced both catalytically and with lithium aluminum hydride. In all cases isotopic fractionation was encountered. The catalytic reductions are of particular interest in that carbon isotope effects have not yet been reported during heterogeneous catalytic processes.

To maximize the validity of our results we have studied our reductions from both ends of the scale of completeness of reaction. That is, we have conducted the reactions to 10% completion, examining the product of 10% reduction, then conducted the reaction to 90% completion, examining the 10% of unreduced product. Quantitative physical and/or chemical methods previously worked out on known mixtures were employed for separation of unreacted material and reaction product, and all radiochemical comparisons were made on the basis of solid crystalline derivatives of known physical properties. The results of our reduction experiments are shown in Table I and Table II.

Examination of Table I reveals that stilbene-α-C^{14} is reduced approximately 0.98 as rapidly as unlabeled stilbene, independently of the catalyst and solvent employed. Table II shows that the isotope effect involved in the catalytic reduction of acetophenone-α-C^{14} (12%) is markedly larger than that observed with stilbene-α-C^{14}, and indicates further that the reduction process need not involve heterogeneous catalysis for isotopic fractionation. The lithium aluminum hydride reduction shows an isotope effect of 8.5%.

TABLE I

ISOTOPE EFFECT DURING CATALYTIC REDUCTION OF STILBENE-α-C^{14}

Stilbene-α-C^{14} assay, mc./mole	Catalyst	Solvent	Completion, %	Product assayed	Assay of product, mc./mole
1.076	Raney Ni	Benzene	10	Bibenzyl-α-C^{14}	1.054
1.076	Raney Ni	Benzene	90	Benzaldehyde-α-C^{14} 2,4-dinitrophenylhydrazone	1.097
2.654	Pt	Ethanol	11	Bibenzyl-α-C^{14}	2.596

TABLE II

ISOTOPE EFFECT DURING REDUCTION OF ACETOPHENONE-α-C^{14}

Acetophenone-α-C^{14} assay, mc./mole	Catalyst	Solvent	Completion, %	Product assayed	Assay of product, mc./mole
2.626	Pt	Ethanol	10	α-Phenylethyl-α-C^{14} 3,5-dinitrobenzoate	2.311
2.626	Pt	Ethanol	90	Acetophenone-α-C^{14} 2,4-dinitrophenylhydrazone	3.237
2.974	($LiAlH_4$)	Ether	15	α-Phenylethyl-α-C^{14} 3,5-dinitrobenzoate	2.720

One feature about the above catalytic processes which might invalidate any interpretation as to the magnitude of isotopic fractionation during heterogeneous catalysis is the possibility of equilibration reactions. Thus with stilbene-α-C^{14} a catalytic equilibration such as (1) between product and reactant would cause the hydrogenation isotope effect

$$PhCH{=}^{*}CHPh + PhCH_2CH_2Ph \overset{\text{cat.}}{\rightleftarrows} PhCH{=}CHPh + PhCH_2CH^{*}{}_2Ph \quad (1)$$

to have an apparent value lower than the actual value. In fact, it readily can be shown mathematically that if (1) occurred at a rate exceeding that of the hydrogenation, and if the equilibrium constant for (1) were unity, no hydrogenation isotope effect would be observable at all. That is, the radioactivity of starting material, unreacted starting material and product would be identical regardless of the extent of hydrogenation or the magnitude of the isotope effect during hydrogenation. We have examined the possibility of an equilibration such as (1) by submitting stilbene-α-C^{14} and non-radioactive bibenzyl to the action, in the absence of hydrogen, of one of our catalysts. Separation and assay of the two molecular species indicated a complete lack of equilibration under the conditions employed. Similarly, when acetophenone-α-C^{14} and non-radioactive 1-phenylethanol were stirred in alcoholic solution with platinum, the recovered acetophenone was found unchanged in its radioactivity assay. Thus equilibration processes such

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(2) W. A. Bonner and C. J. Collins, THIS JOURNAL, **75**, 2308 (1953).

(3) W. A. Bonner and C. J. Collins, *ibid.*, **75**, 3693 (1953).

as (2) and (3) similarly do not appear to occur under the influence of a hydrogenation catalyst.

$$\text{Ph*COCH}_3 + \text{PhCH(OH)CH}_3 \overset{\text{cat.}}{\rightleftarrows} \text{Ph*CH(OH)CH}_3 + \text{PhCOCH}_3 \quad (2)$$

$$\text{Ph*COCH}_3 + \text{C}_2\text{H}_5\text{OH} \overset{\text{cat.}}{\rightleftarrows} \text{Ph*CH(OH)CH}_3 + \text{CH}_3\text{CHO} \quad (3)$$

Further data substantiating these results were obtained under actual hydrogenation conditions. Non-radioactive stilbene was hydrogenated to 50% completion in the presence of a tenfold excess of bibenzyl-α-C^{14} after which the unreacted stilbene was found still to be totally void of radioactivity. It thus appears that equilibration processes of the sort discussed occur, if at all, much more slowly than catalytic reduction and that our data regarding isotopic fractionation during heterogeneous catalysis may be interpreted as being uncomplicated by the occurrence of competing equilibration processes.

It is not possible with the present data to decide whether our observed isotopic fractionation during heterogeneous catalysis occurs during adsorption onto the catalyst surface of the species undergoing reduction or during actual addition of hydrogen to the adsorbed molecule. It is hoped that future investigation of such reactions might permit such a distinction to be made unambiguously.

Experimental

10% Hydrogenation of Stilbene-α-C^{14}.—Stilbene-α-C^{14} (1.1484 g.) (radioactivity assay[4] 1.076 ± 0.0000 mc./mole) was dissolved in dry benzene (35 ml.), and the solution treated with 0.07 g. of Raney nickel.[5] The mixture was placed in a 50-ml. buret hydrogenator, and hydrogenated with stirring; temp. 26°, press. 738.6 mm. In seven minutes 18.75 ml. of hydrogen (10%) was consumed. The catalyst was filtered and rinsed and the filtrate was evaporated to dryness. The majority of unreduced stilbene was removed from the residue by recrystallization from ethanol (15 ml.); 0.8230 g. of somewhat impure stilbene, m.p. 122.5–124°, resulted. The mother liquors were again evaporated dry and the residue dissolved in acetone (45 ml.). To this solution was added dropwise with stirring a solution of potassium permanganate (1 g.) and magnesium chloride (0.5 g.) in water (10 ml.). Stirring was continued for 40 minutes, after which the excess permanganate was destroyed by addition of sufficient sodium bisulfite solution. The MnO_2 was filtered and rinsed with acetone. The filtrate was diluted with water, then placed on the steam-bath to boil away the majority of the acetone. The aqueous remainder was salted and extracted twice with ether. The extract was clarified with Norit and the solvent distilled, yielding 0.15 g. of oil. This was recrystallized twice from dilute ethanol to give a total of 0.075 g. of bibenzyl-α-C^{14}, m.p. 52.5–53.5°. This, as well as all samples below, was dried *in vacuo* over phosphoric anhydride prior to assay; radioactivity assay 1.054 ± 0.004 mc./mole.

In another experiment 0.10 g. of Adams catalyst was reduced in 10 ml. of ethanol, then rinsed into a hydrogenation flask containing 1.1484 g. of stilbene-α-C^{14} (radioactivity assay 2.654 ± 0.002 mc./mole) dissolved in 160 ml. of ethanol. Hydrogenation with 18.4 ml. (11%) of hydrogen (27.5°, 739 mm.) took four minutes. The reaction mixture was processed as described above, removing the majority of unreacted stilbene by crystallization, and the remainder by oxidation with permanganate. The crude yield of bibenzyl-1-C^{14} was 0.0841 g. (73%). Recrystallization gave 0.0472 g. of m.p. 52–53° and radioactivity assay 2.596 ± 0.004 mc./mole.

90% Hydrogenation of Stilbene-α-C^{14}.—When an attempt was made to hydrogenate stilbene to 90% completion with Raney nickel on the basis of the calculated volume of hydrogen the results were found unreliable, presumably due to the hydrogen adsorbed on the Raney nickel surface during its preparation.[6] Consequently 0.5000 g. of non-radioactive stilbene was dissolved in benzene (15 ml.), 0.07 g. of Raney nickel was added, and hydrogenation carried to completion; 66.9 ml. was consumed in 20 minutes. Immediately following this experiment 0.5000 g. of stilbene-α-C^{14} (radioactivity assay 1.076 ± 0.000 mc./mole) was hydrogenated under identical conditions to a hydrogen volume uptake of 58 ml. (87%). The catalyst was filtered, rinsed with benzene, and the filtrate evaporated to dryness. The residue was dissolved in ethanol (10 ml.) and the solution ozonized[7] for a period of 10 minutes, then treated with a hot solution of 2,4-dinitrophenylhydrazine (0.15 g.) and sulfuric acid (1 ml.) in ethanol (2 ml.) after adding a seed of benzaldehyde 2,4-dinitrophenylhydrazone. After cooling, the solid derivative was filtered, rinsed with ethanol and dried, 0.1481 g. Assuming a quantitative yield, this corresponds to 0.0465 g. of unreacted stilbene-α-C^{14}, or a 93% complete hydrogenation. The product was recrystallized from 3.8 ml. of purified dioxane[8] to give 0.1027 g. of pure benzaldehyde-α-C^{14} 2,4-dinitrophenylhydrazone, m.p. 239–240°. Radioactivity assay was conducted by the usual wet combustion procedure[9] modified by inclusion of a lead peroxide cartridge in the combustion line to remove the nitrogen oxides produced.[3] The value found was 1.097 ± 0.003 mc./mole after multiplication by the factor of 2 required for comparing stilbene-α-C^{14} with its benzaldehyde degradation product.

The ozonization mother liquors from the above and a similar hydrogenation were diluted with water, salted and stirred. The solid was filtered, and the yellow cake steam distilled to free the bibenzyl-α-C^{14}. Ether extraction of the salted steam distillate led to an 80% recovery of bibenzyl-α-C^{14} which was purified by recrystallization from dilute ethanol; radioactivity assay 1.073 ± 0.002 mc./mole, in good agreement with the starting stilbene-α-C^{14}.

Attempted Catalytic Equilibration of Stilbene-α-C^{14} with Non-radioactive Bibenzyl.—Raney nickel (0.07 g.) was stirred with non-radioactive stilbene (1 g.) in benzene (25 ml.) for one hour to remove surface adsorbed hydrogen. The solvent was decanted and the catalyst rinsed several times with benzene. To the catalyst in benzene (20 ml.) was added stilbene-α-C^{14} (0.400 g.) (radioactivity assay 1.076 ± 0.000 mc./mole) and non-radioactive bibenzyl (0.400 g.). The mixture was stirred at room temperature for 30 minutes, after which the catalyst was filtered and rinsed with benzene. The filtrate was evaporated to dryness. The residue was dissolved in acetone (100 ml.), and the solution treated dropwise with stirring with a solution of potassium permanganate (2 g.) and magnesium chloride (1 g.) in water (25 ml.). The mixture was stirred for an hour at 25°, after which the excess permanganate was destroyed by addition of sufficient sodium bisulfate solution. The MnO_2 was filtered and rinsed with acetone and hot water and the filtrate was boiled to remove most of the acetone. Sodium bicarbonate was added to the residual aqueous mixture, which was then extracted three times with ether. Evaporation of the ether layer, followed by Norit decolorization, led to a quantitative yield of crude bibenzyl, m.p. 53.5–54° after recrystallization from dilute ethanol. This material was non-radioactive to the Geiger tube. The aqueous layer from the above ether extraction was acidified, then extracted three times with ether. Solvent removal, followed by Norit decolorization, gave an 81% yield of crude benzoic-*carboxy*-C^{14} acid. This was recrystallized from water to give a sample of correct m.p. showing a radioactivity assay of 1.071 ± 0.001 mc./mole after multiplication by the factor of 2 required for comparing stilbene-α-C^{14} with its benzoic acid degradation product.

Attempted Equilibration of Stilbene with Bibenzyl-α-C^{14} under Hydrogenation Conditions.—Non-radioactive stilbene (0.1800 g., 1 millimole) and bibenzyl-α-C^{14} (1.8200 g.,

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[4] All assays run in duplicate are reported with average deviation from mean value.

[5] R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

[6] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943).

[7] W. A. Bonner, *J. Chem. Ed.*, in press.

[8] L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Company, New York, N. Y., 1941, p. 368.

[9] O. K. Neville, THIS JOURNAL, **70**, 3501 (1948).

10 millimoles; radioactivity assay 0.295 mc./mole) were dissolved in ethanol (25 ml.) containing freshly reduced Adams catalyst (0.05 g.). Hydrogenation to 50% completion (14.10 ml., 26.5°, 737.5 mm.) took about 30 minutes on the buret hydrogenator. The catalyst was filtered and rinsed and the filtrate was subjected to ozonolysis for 15 minutes. Some bibenzyl-α-C^{14} precipitated toward the end of the ozonization due to cooling; this was redissolved by warming. To the ozonized mixture was added a seed of benzaldehyde 2,4-dinitrophenylhydrazone, followed by a solution of 2,4-dinitrophenylhydrazine (0.25 g.) and sulfuric acid (1.5 ml.) in ethanol (2 ml.). Precipitation of the derivative was instantaneous. The 0.307 g. of derivative was recrystallized twice from dioxane (8 ml.) to give 0.183 g. of pure benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 238–238.5°. Wet combustion of this sample produced carbon dioxide whose radioactivity was indistinguishable from background.

10% Hydrogenation of Acetophenone-α-C^{14}.—Acetophenone-α-C^{14} was converted to its 2,4-dinitrophenylhydrazone in the usual way. Recrystallization from dioxane gave an 88% yield of material having m.p. 248–249° and showing a radioactivity assay of 2.626 ± 0.007 mc./mole (PbO_2 cartridge in combustion line). This acetophenone-α-C^{14} was used in the experiments described below unless otherwise noted.

Adams catalyst (0.10 g.) was reduced in ethanol (10 ml.), then washed into a solution of 2.0323 g. of acetophenone-α-C^{14} in ethanol (25 ml.). The mixture was hydrogenated (27°, 741 mm.) to a volume of 46.9 ml. (10%) in the usual buret apparatus. The catalyst was filtered and rinsed and the filtrate cautiously evaporated almost to dryness at 100° in an air stream. The remaining solvent was removed by evacuation, and the 1.6859 g. of residue dissolved in 25 ml. of benzene. This solution was passed through a 1 × 20 cm. column of alumina, rinsing with 100 ml. of benzene. Evaporation of the benzene effluent gave 1.3583 g. (74% of unreacted acetophenone-α-C^{14}. The column was next rinsed with 100 ml. of ethanol. Evaporation led to 0.1448 g. (70%) of crude α-phenylethylethanol-α-C^{14}. This was dissolved in pyridine (3 ml.), and the solution treated with 0.40 g. (50% excess) of freshly prepared 3,5-dinitrobenzoyl chloride. After heating for 10 minutes the solution was poured into water, and the α-phenylethyl-α-C^{14} 3,5-dinitrobenzoate isolated by ether extraction in 46% crude yield (0.1703 g.). Two recrystallizations from ethanol gave 0.0484 g. of pure material, m.p. 99–100° in agreement with the literature[10]; radioactivity assay 2.311 ± 0.000 mc./mole.

90% Hydrogenation of Acetophenone-α-C^{14}.—Adams catalyst (0.10 g.) was reduced in ethanol (10 ml.) then rinsed with 15 ml. of ethanol into a hydrogenation flask containing 1.0245 g. of acetophenone-α-C^{14}. Reduction was conducted in the usual apparatus (26°, 743 mm.) to a volume of 210.6 ml. (90%). The catalyst was filtered and rinsed, and the filtrate evaporated to dryness. The 0.8022 g. (78%) of oil recovered was dissolved in ethanol (4 ml.) and treated with a solution of 2,4-dinitrophenylhydrazine (0.25 g.) and sulfuric acid (1.5 ml.) in hot ethanol (2 ml.). The acetophenone-α-C^{14} 2,4-dinitrophenylhydrazone obtained weighed 0.0801 g. Recrystallization from 2.5 ml. of purified dioxane gave 0.0686 g. of red needles, m.p. 247.5–248°, radioactivity assay 3.237 ± 0.001 mc./mole.

Attempted Catalytic Equilibrium between Acetophenone-α-C^{14} and Non-radioactive α-Phenylethanol.—Adams catalyst (0.10 g.) was reduced in ethanol, then rinsed with 20 ml. of ethanol into a mixture of 0.500 ml. of α-phenylethanol and 0.500 ml. of acetophenone-α-C^{14} (radioactivity assay 2.974 ± 0.006 mc./mole). The mixture was stirred for one hour at room temperature, after which the catalyst was filtered and rinsed with ethanol. The filtrate was treated with a hot solution of 2,4-dinitrophenylhydrazine (0.92 g., 10% excess) and sulfuric acid (2 ml.) in ethanol (3 ml.). The crude acetophenone-α-C^{14} 2,4-dinitrophenylhydrazone weighed 1.2556 g. (97.4%) and was recrystallized from 32 ml. of purified dioxane. The purified product weighed 1.1232 g., had m.p. 247–248°, and showed a radioactivity assay of 2.969 ± 0.001 mc./mole.

Partial Reduction of Acetophenone-α-C^{14} with Lithium Aluminum Hydride.—A slurry of lithium aluminum hydride in ether was stirred for a prolonged period, filtered (Celite), and the cake rinsed with dry ether. The solution was standardized approximately by pipetting 2.00 ml. into a hydrogenation flask, placing in position on a buret hydrogenator, decomposing the hydride by addition of excess ethanol, and noting the hydrogen volume; 40.5 ml. was produced.

Acetophenone-α-C^{14} (1.553 g. radioactivity assay 2.974 ± 0.006 mc./mole) was dissolved in dry ether (15 ml.) and the solution treated dropwise with stirring with 2.00 ml. of the above lithium aluminum hydride solution (enough for 14.4% reduction). The mixture was diluted with ether, shaken with dilute hydrochloric acid, and the ether layer evaporated, giving 1.371 g. (88%) of oil. This was dissolved in hexane (25 ml.) and passed through a 1 × 20 cm. alumina column, rinsing with 100 ml. of hexane. Solvent evaporation through a small fractionating column gave 0.955 g. of recovered acetophenone-α-C^{14}. The column was then rinsed with 100 ml. of methanol and the solvent evaporated from the effluent, leaving 0.174 g. of α-phenylethanol-C^{14}. Assuming equal yields on the two fractions, this figure corresponds to 15.4% reduction of the original ketone. The carbinol reduction product was converted to its 3,5-dinitrobenzoate ester in the manner previously described. After two recrystallizations from ethanol the ester had a m.p. of 96–97° and showed a radioactivity assay of 2.720 mc./mole.

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[10] W. Reppe, O. Schlichting, K. Klager and T. Toepel, *Ann.*, **560**, 48 (1948).

[11] *Cf.* G. A. Ropp, V. F. Raaen and A. J. Weinberger, THIS JOURNAL, **75**, 3695 (1953).