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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Relative Extents of Catalytic Hydrogen–Deuterium Exchange in the Nuclear Positions of Phenylacetamide[1,2]

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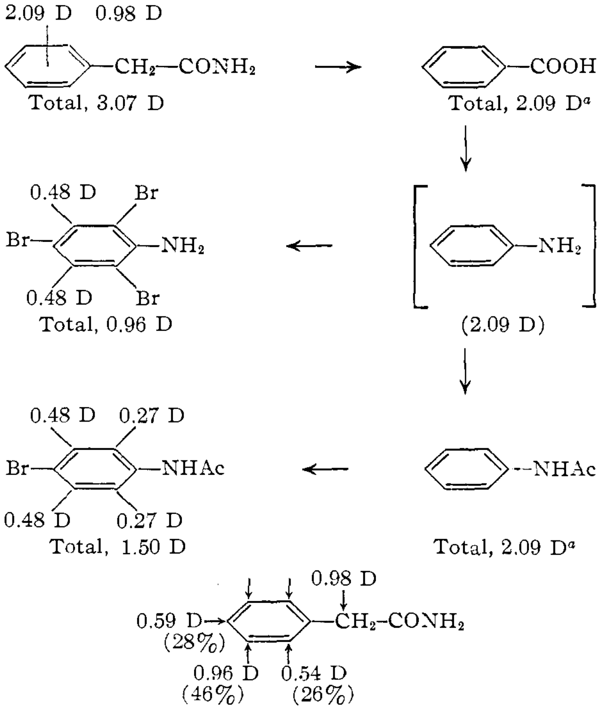
When phenylacetamide was treated with deuterated Raney nickel in refluxing deuteroethanol, 49% of the α-hydrogens and 42% of the nuclear hydrogens underwent hydrogen–deuterium exchange. The product was degraded to aniline, and various nuclear positions of the aniline were selectively brominated. Deuterium assays of the brominated samples indicated the nuclear deuterium distribution as 26% *ortho*-, 46% *meta*- and 28% *para*-. Repetition of this deuteration in benzene solvent for thrice the reaction time led to H–D exchange at only 6.5% of the α-hydrogens and 2.6% of the nuclear hydrogens of phenylacetamide. These results are discussed briefly with regard to the mechanism of nuclear H–D exchange under these catalytic conditions.

Recently we reported[3] that both α-hydrogen and nuclear hydrogen atoms in mandelamide and phenylacetamide undergo exchange with deuterium on treatment with deuterated Raney nickel catalyst in refluxing deuteroethanol. When these studies were extended to optically active 2-phenylpropionamide, it was found[4] that such exchange processes occurred more rapidly than did racemization, indicating a certain stereospecificity for such exchange reactions. This stereospecificity, as well as the occurrence of ring and methyl-group exchange, were tentatively rationalized[4] in terms of a stereospecifically adsorbed carbonium ion intermediate. Ethylbenzene was similarly shown[4] to undergo nuclear hydrogen–deuterium exchange under the same conditions.

If nuclear H–D exchange occurred as postulated[4] *via* a benzyl type carbonium ion intermediate and its nuclear canonical stabilizing structures, then nuclear H–D exchange ought to occur predominantly in the *o*- and *p*-positions of the aromatic ring. In order to test this hypothesis we have again engendered α-position and nuclear H–D exchange in phenylacetamide by the action of deuterated Raney nickel in refluxing deuteroethanol. The deuterated phenylacetamide product was oxidized to benzoic acid, and deuterium assays of the two substances provided an indication of nuclear *vs.* chain deuteration. The relative extents of ring deuteration at the *o*-, *m*- and *p*-positions of the benzoic acid product were determined by conversion of the latter to aniline, then by selective bromination of appropriate derivatives of the aniline, followed by deuterium assay of the bromination products. The results of these experiments are indicated in Table I, and the conclusions regarding relative positions of H–D exchange reached therefrom are summarized in Chart I.

Chart I indicates approximately 1:1.8:1.1 ratios, respectively, for the *o*, *m*- and *p*-distribution of deuterium atoms in the phenyl nucleus of phenylacetamide. Ratios for random nuclear exchange would be 2:2:1. It is interesting to compare these results with those of Lauer and Errede[5] who studied the action of Raney alloy in refluxing deuterium oxide with sodium deuteroxide on aniline. Using similar techniques, they found exchange ratios of about 6.5:1.0:1.2, respectively, for the *o*-, *m*- and *p*-positions of aniline under these conditions. The predominant exchange at the *o*-position was attributed to the anchoring of the aniline molecule to the catalyst through the electron pair of nitrogen, thus locating the *o*-hydrogens sterically in the most favorable position for exchange.

CHART I
DEUTERIUM DISTRIBUTION IN DEUTERATED PHENYLACETAMIDE



[a] Average value for two benzoic acid and one acetanilide assays.

From the data in Table I and Chart I it is clear that there is no marked selectivity for any specific nuclear position in the catalytic H–D exchange of phenylacetamide. This argues against such nu-

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(1) This constitutes Communication IX in the series "The Stereochemistry of Raney Nickel Action."

(2) We are grateful to the Petroleum Research Fund Advisory Board of the American Chemical Society for its support of a portion of this research.

(3) W. A. Bonner, THIS JOURNAL, **76**, 6350 (1954).

(4) W. A. Bonner and J. A. Zderic, *ibid.*, **78**, 4369 (1956).

(5) W. M. Lauer and L. A. Errede, *ibid.*, **76**, 5162 (1954).

TABLE I

DEUTERIUM CONTENTS OF PRODUCTS FROM EXPERIMENTS ON THE DEUTERATION OF PHENYLACETAMIDE

No.	Reactant	Product	Product combustion water		Hydrogen-deuterium relationships		Product, gram-atoms per mole	
			% D_2O	% H_2O	D/H[c]	D + H[d]	D	H
1	Phenylacetamide[a]	Phenylacetamide-*d*	36.5	63.5	0.517	9	3.07	5.93
2	Phenylacetamide-*d*	Benzoic acid-*d*	35.1	64.9	.487	6	1.93	4.07
3	Benzoic acid-*d*	Acetanilide-*d*	26.0[e]	74.0[c]	.316[e]	9	2.16	6.84
4	Benzoic acid-*d*	2,4,6-Tribromoaniline-*d*	26.2	73.8	.320	4	0.96	3.04
5	Acetanilide-*d*	*p*-Bromoacetanilide-*d*	20.4	79.6	.231	8	1.50	6.50
6	Phenylacetamide[b]	Phenylacetamide-*d*	3.1	96.9	.0288	9	0.26	8.74
7	Phenylacetamide-*d*	Benzoic acid-*d*	2.5	97.5	.0230	6	.13	5.87
8	Benzene	Benzene-*d*	2.3	97.7	.0212	6	.12	5.88
		Diphenyl-*d*	2.3	97.7	.0212	10	.20	9.80

[a] Reaction employing deuterated Raney nickel in absolute C_2H_5OD. [b] Reaction employing deuterated Raney nickel in benzene. [c] Obtained from the relation $18 \times \% D_2O/20 \times \% H_2O = D/H$. [d] Total number of H-species atoms in the product molecule. [e] Average of two determinations.

clear exchange resulting as a consequence of resonance stabilization of a benzylcarbonium ion intermediate as previously hypothesized[4] and suggests rather that nuclear H–D exchange here is a more or less random process occurring *independently* of any additional exchange taking place at the α-carbon. Also, by Lauer's argument, our relatively low value for exchange at the *o*-positions indicates that the benzyl carbon was in all probability in no way involved in attaching the molecule to the catalyst surface. The lower than statistical exchange value at the *o*-positions, in fact, argues that steric factors in phenylacetamide or in its adsorption on the catalyst surface are actually such as to hinder exchange at these positions.

These tentative conclusions receive some support from the data of experiments, 6, 7 and 8 in Table I. When phenylacetamide was treated with deuterated Raney nickel in refluxing benzene (18 hr.) instead of deuteroethanol (6 hr.), considerably less H–D exchange occurred, both at the α-carbon and in the nucleus. The benzoic acid derived from this deuterated phenylacetamide sample contained only about 6% as much deuterium as previously observed, or 0.13 gram-atom of deuterium per mole. Benzene itself, when refluxed with deuterated Raney nickel (30 hr.), underwent H–D exchange to the extent of 0.12 gram-atom per mole. In this reaction a trace (1–3%) of biphenyl was produced, which proved to have about the same deuterium content per nucleus as did the benzene, *i.e.*, 0.20 gram-atom per mole. The comparable extents of H–D exchange for benzene and the nucleus of phenylacetamide indicate that, in benzene solvent at least, the side chain of phenylacetamide plays a negligible part in the nuclear H–D exchange process. Further exchange experiments on systems of this type are currently in progress.

In view of the small amount of exchange occurring catalytically with phenylacetamide in benzene solution, we have again[3] attempted the dehydroxylation of optically active mandelamide to produce optically active α-deuterophenylacetamide. When L(+)-mandelamide was treated with deuterated Raney nickel in refluxing benzene solution for 5 hr., the phenylacetamide recovered proved, however, to be optically inactive.

Experimental

Deuterated Raney Nickel. Sample A.—About 50 g. of Raney nickel[6] was equilibrated three times for 24-hr. periods with heavy water (30-ml. portions) (recovered from previous experiments[4]; distilled from a trace of sodium hydroxide; containing some dioxane), then for 2.5 days with 18 ml. of 99+% deuterium oxide. The catalyst so prepared was filtered damp-dry by suction immediately prior to its use.

Sample B.—Freshly prepared Raney nickel[6] was filtered damp-dry (55 g.) on a sintered funnel, then treated with thorough mixing with 8 ml. of 99+% deuterium oxide having d^{20} 1.077. After two days the mixture was sucked damp-dry at the aspirator, then treated with thorough mixing with an additional 8 ml. of 99+% D_2O. The filtrate had d^{20} 1.038. After a second 2-day period the mixture was again filtered damp-dry and treated with an additional 8 ml. of 99+% D_2O. The second filtrate had d^{20} 1.064. After seven days the mixture was again sucked damp-dry, and the filtrate was found to have d^{20} 1.077. The catalyst sample was assumed at this point to be completely deuterated and was used without further equilibration.

Deuterated Raney Nickel with Phenylacetamide.—Phenylacetamide (6.00 g.) was dissolved with heating in absolute deuteroethanol[3] (34 ml.), whereupon the entire sample A of deuterated Raney nickel was added after sucking damp-dry from its final equilibration rinse. The mixture was heated under reflux (calcium chloride tube protection) with occasional swirling during an 8-hr. period, then filtered on a sintered funnel. The filter cake was rinsed thoroughly with ethanol and acetone, then sucked damp-dry (50 g.). The filtrate was evaporated to dryness, and the residue was dissolved in ethanol (100 ml.) to exchange $-ND_2$ for $-NH_2$. The solution was again evaporated, to yield 5.64 g. (94%) of deuterated phenylacetamide. A small portion of this product was recrystallized from a mixture of ethanol and ligroin to provide a sample for deuterium assay. The deuterium content was measured as previously[3] by combustion, collection of the combustion water and mass spectrographic assay of the latter[7]; combustion water, % D_2O, 36.5.

Hydrolysis and Oxidation of Deuterated Phenylacetamide.—The above deuterated phenylacetamide (5.57 g.) was stirred under reflux with 10% sodium hydroxide solution (100 ml.) and glass beads. After ten minutes, solution of the amide was complete, and potassium permanganate (10 g.) was gradually added to the reaction mixture. After initial foaming had subsided, an additional 10 g. of potassium permanganate was added, and the mixture was stirred under reflux during 2 hr. Excess sodium sulfite was added to destroy residual permanganate, and the mixture was filtered to remove MnO_2. The cake was rinsed well with water, and the filtrate was acidified. The precipitated benzoic acid was filtered, and the filtrate was extracted four

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(6) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(7) Mass spectrographic analyses of the combustion water from this and the remaining samples were conducted by Dr. H. Eding and Mr. C. Lanpher of Stanford Research Institute.

times with C.P. ether. The extract was washed, dried and evaporated. The total crude benzoic acid weighed 4.78 g. (95%). A sample of this acid was recrystallized (Norit) from water, then sublimed *in vacuo* prior to assay, m.p. 121.5–122.5°; combustion water, % D_2O, 35.1.

Deuterated Benzamide.—The above deuterated benzoic acid (4.06 g.) was converted to benzamide by refluxing with thionyl chloride, followed by treatment of the residue therefrom with chilled ammonium hydroxide. The crude amide was recovered in 1.60 g. (40%) yield. It was recrystallized from a mixture of ethanol (1 ml./g.) and ligroin (3 ml./g.) to yield two crops: (1) 1.26 g., m.p. 126–127° and (2) 0.25 g., m.p. 121–123.5°.

Hofmann Degradation of Diluted Deuterated Benzamide.—1.487 g. of the above deuterated benzamide was diluted with 1.487 g. of recrystallized stock benzamide. The mixture was treated with a solution of potassium hydroxide (4.2 g.) and bromine (1.42 ml.) in water (38 ml.). The mixture was swirled thoroughly, then treated with a solution of potassium hydroxide (5.9 g.) in water (10 ml.). The temperature was maintained at 70–80° for 35 minutes, whereupon the mixture was steam distilled, collecting 75 ml. of distillate. The distillate was salted and extracted four times with ether. The extract was dried over potassium hydroxide, filtered and freed of solvent through a small column. The residue was 2.24 g. (98%) of crude aniline.

Deuterated Tribromoaniline.—Bromine (0.5 ml.) in acetic acid (3 ml.) and water (2 ml.) was added with stirring to 0.3 ml. of the above aniline dissolved in a mixture of acetic acid (2 ml.) and water (3 ml.). After five minutes the mixture was diluted with water, and the crude tribromoaniline (0.95 g., 89%) was collected. The latter was recrystallized twice (Norit) from dilute ethanol, to give 0.29 g. of a sample having m.p. 119.5–120°; combustion water, % D_2O, 13.1; corrected for dilution, 26.2%.

Deuterated Acetanilide.—One and nine-tenths grams of the above aniline was converted to acetanilide by the method described by Fieser.[8] The crude product was obtained in 1.13 g. (41%) yield. A sample was purified by vacuum sublimation prior to deuterium assay, m.p. 113.5–114.5°; combustion water, % D_2O, 13.5, 12.5; corrrected for dilution, 26.0%.

Deuterated *p*-Bromoacetanilide.—One gram of the above acetanilide was brominated according to the procedure of Fieser,[9] using proportional reagent quantities. The crude product, 1.51 g. (95%), was recrystallized twice from dilute ethanol prior to deuterium assay, m.p. 167–167.5°; combustion water, % D_2O, 10.2; corrected for dilution, 20.4%.

Action of Deuterated Raney Nickel on Benzene.—About 4 g. of the above sample B deuterated Raney nickel was sucked damp-dry and treated with 40 ml. of azeotropically dried benzene. The mixture was distilled to a small volume, then treated with additional benzene and distilled to a residual volume of about 10 ml. At this point the clumped catalyst had become evenly dispersed through the solvent, no more D_2O was apparent in the distillate and the catalyst was quite pyrophoric. The mixture was refluxed during 30 hr., then filtered damp-dry. The residual catalyst was markedly pyrophoric. Odor and infrared examination of the filtrate suggested the presence of a product other than benzene. Evaporation of 5.38 g. of the filtrate left a pasty residue of 0.07 g. (1.3%). This smelled like biphenyl and was purified twice by sublimation at 70° (0.5 mm.). The white sublimate had m.p. 69–70° and showed no mixed m.p. depression with a sublimed sample of biphenyl (m.p. 69–70°). In another experiment 2.40 g. of the above filtrate left 0.08 g. (3.7%) of crude biphenyl. This was purified by sublimation and combusted for deuterium assay; combustion water, % D_2O, 2.3.

A 0.25-ml. sample of the above benzene filtrate was freed of its deuterated biphenyl by passage through a 4-foot Celite–Silicone vapor phase chromatographic column.[10] The benzene fraction was collected[10] and combusted for deuterium assay; combustion water, % D_2O, 2.3.

Deuterated Raney Nickel in Benzene on Phenylacetamide.—A portion of sample B deuterated Raney nickel above was sucked damp-dry (25 g.). The damp sample was added to azeotropically topped benzene (300 ml.), and the mixture was distilled down to 60 ml., driving off the majority of residual D_2O and giving a uniform suspension of catalyst. Phenylacetamide (6.00 g.) and dry benzene (10 ml.) were added, and the mixture was refluxed for 18 hr. under $CaCl_2$-tube protection. The hot mixture was filtered and the cake was rinsed twice with boiling benzene and five times with boiling acetone. Solvent evaporation left 5.40 g. (90%) of product. A portion thereof was recrystallized twice from an ethanol–ligroin mixture, m.p. 157–158°; combustion water, % D_2O, 3.1.

In a separate experiment it was found that ordinary Raney nickel in benzene had no readily detectable chemical action on phenylacetamide during 65 hr. of refluxing.

Hydrolysis and Oxidation of Deuterated Phenylacetamide.—A 5.20-g. portion of the above deuterated phenylacetamide was hydrolyzed as before with refluxing 10% sodium hydroxide solution (100 ml.), then oxidized by treatment with excess potassium permanganate. Usual processing led to 4.11 g. (87.5%) of benzoic acid. A portion was recrystallized from water and sublimed prior to deuterium assay; combustion water, % D_2O, 2.5.

Deuterated Raney Nickel in Benzene on L(+)-Mandelamide.—Deuterated Raney nickel (sample B, 23 g. damp weight) was treated with dry benzene (200 ml.). The mixture was azeotropically dried by distillation to a volume of 60 ml., then treated with 1.00 g. of L(+)-mandelamide ($[\alpha^{25}]_D$ +69.0° (*c* 2, acetone), 96% optically pure). The mixture was refluxed for 5.2 hr., and the product (0.40 g.) was isolated as usual. It was dissolved in ethanol, and the solution was allowed to stand 18 hr., then evaporated to dryness. Two recrystallizations (Norit) from a mixture of ethanol and ligroin produced phenylacetamide having m.p. 157.5–158° and showing no optical activity beyond experimental error in acetone solution (*c* 3).

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[8] L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 165.

[9] Reference 8, p. 167.

[10] W. A. Bonner and T. W. Greenlee, THIS JOURNAL, **79**, 1696 (1957).

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[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, KYOTO UNIVERSITY]

The Dipole Moments and Molecular Structures of *ac-trans*-Dihalogenotetralins[1]

BY TOSHIO FUJITA

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The dipole moments of 2,3-dihalogenotetralins and 1,2-dihalogenotetralins were measured in solution at various conditions, to show that each of these compounds has a half-chair ring and can occur in two conformations which are in equilibrium through ring conversion. Then, the energy difference ΔE between the two conformations of each compound is estimated. From comparison of the ΔE values, it is concluded that the properties of 2,3-dihalogeno compounds are very similar to those of corresponding dihalogenocyclohexenes, and the *aa* conformation of the 1,2-isomers is more stable than that of the 2,3-isomers.

The concept of "non-bonded energy"[2] in cyclohexane derivatives has given clear explanations to

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[1] Presented at the monthly meeting of Kansai Branch of the Agricultural Chemical Society of Japan, Kyoto, June 23, 1956.

[2] W. Klyne, "Progress in Stereochemistry," Vol. I, W. Klyne, Ed., Butterworths Scientific Pub., London, 1954, p. 36.