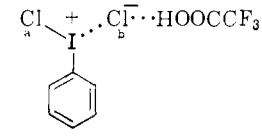
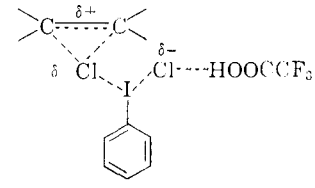
As described in the Experimental section, the products of reaction of the dichloride with both stilbene and cyclohexene, as formed by reaction at concentration levels of the catalyst and the reactants similar to those used in the rate studies, have been investigated qualitatively. In neither case have exclusively *cis* addition products been found. Stilbene (the *trans* isomer) reacts to form substantial quantities of *meso* as well as of *dl*-stilbene dichloride and also an appreciable amount of chlorotrifluoroacetate, $C_6H_5CHClCH(OCOCF_3)$-C_6H_5. The product from cyclohexene is completely free of *cis* adducts. The only identifiable organic substances which it has been found to contain are *trans*-1,2-dichlorocyclohexane and *trans*-1 - trifluoroacetoxy - 2 - chlorocyclohexane. It has been demonstrated that the isomeric dichlorides of stilbene and of cyclohexane are stable under the conditions of the addition reactions.

Qualitatively these reactions products are similar in composition to those formed when free chlorine is substituted for iodobenzene dichloride as the halogen source. The procedures devised for analysis of the reaction products are not sufficiently precise so that even a semi-quantitative comparison of the relative amounts of the various adducts formed from the dichloride and from free chlorine can be made. It is probable, however, that the product composition is subject to some change with the change in halogen source. Very likely it also varies appreciably with changes in the concentrations of the reactants and the catalyst, although no very reliable supporting data have been collected.

The catalytic action of trifluoroacetic acid in promoting the direct reaction of an ethylenic compound with iodobenzene dichloride must be attributed to the capacity of the acid to promote the electrophilic character of one of the halogen atoms of the dichloride molecule (chlorine a) through hydrogen bonding to the other halogen (chlorine b).[5] For the sake of simplicity the acid is represented as the monomer in the formulas accompanying this discussion, although very likely



it is dimeric in character. In the activation process for the slow step of the addition reaction, in which positive halogen must be transferred to the double bond, polarization of the reactants must occur as shown below. At least one more catalyst molecule, in addition to that shown, must be



included in the solvation sphere of this aggregate since the reaction order with respect to the catalyst is second or larger. The intermediate formed in the slow step of the reaction of cyclohexene is presumed to be akin to a cyclic chloronium ion in character, since the products which are formed on further reaction, the dichloride and the trifluoroacetoxy chloride, are exclusively *trans* in character. In the case of the reaction of stilbene the electrophilic chlorine atom apparently provides much less neighboring group protection. There is other evidence[19] that the effectiveness of a neighboring chlorine atom in stabilizing an electron-deficient carbon atom is by no means at a maximum when that carbon bears a phenyl substituent.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research. They wish to thank Professor R. E. Kepner and Mr. J. D. Davis for their assistance with the chromatographic phases of this work.

(19) S. Winstein and D. Seymour, *J. Am. Chem. Soc.*, **68**, 119 (1946).

[CONTRIBUTION FROM THE JAMES BRYANT CONANT LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

The Reduction of Olefinic Double Bonds with Dihydropyridines

BY B. E. NORCROSS, P. E. KLINEDINST, JR., AND F. H. WESTHEIMER

RECEIVED AUGUST 25, 1961

Two dihydropyridines reduce the olefinic double bond of 1-phenyl-4,4,4-trifluoro-2-buten-1-one in good yield under mild conditions. Tracer experiments show that hydrogen is transferred directly from the 4-position of the pyridine ring to the carbon atom beta to the carbonyl group. The reaction thus roughly parallels the enzymatic reduction of androstenedione achieved by McGuire and Tompkins. The model reaction is restricted to activated double bonds, and (among the seven N-alkyl dihydropyridines tried) has succeeded only with 1,3,5-trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine. Specific examples of the reduction of carbon–carbon double bonds by dihydropyridines are presented and discussed.

Diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN) are among the principal coenzymes for biochemical oxidation–reduction reactions. Recently, McGuire and Tompkins[1] have reduced the olefinic double bond of androstenedione with TPNH (reduced triphosphopyridine nucleotide) and an enzyme from rat-liver mitochondria. In this paper, a nonenzymatic model for the reduction of the carbon–carbon double bond of an α,β-unsaturated ketone is presented and discussed.

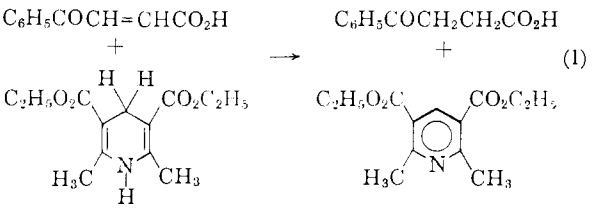
The enzymatic reduction of various carbonyl compounds with DPNH (reduced diphosphopyri-

(1) J. S. McGuire and G. M. Tompkins, *Fed. Proc.*, **19**, A29 (1960).

dine nucleotide) or TPNH takes place stereospecifically[2-4] with direct transfer of hydrogen[5] from the 4-position of the dihydropyridine[6-9] to the substrate. Numerous examples of the reduction of aldehydes, ketones and thioesters by DPNH and TPNH are known,[10,11] but generally the enzymatic reduction of olefinic double bonds has been ascribed to the action of flavins. Although the enzyme obtained by McGuire and Tompkins is part of the particulate fraction and therefore necessarily impure, tracer evidence indicates that TPNH is actually the coenzyme directly involved. When the reduction was conducted in tritiated water, the reduced ketone contained tritium, all of which could be removed by equilibrating the androstanedione with water and alkali. The tritiated water introduced the heavy isotope of hydrogen only at the position alpha to the carbonyl group; the hydrogen beta to the carbonyl group presumably came directly from the TPNH. By contrast, the enzymatic reduction of orotic acid to dihydroörotic acid,[12] which consumes DPNH, must nevertheless involve some other coenzyme (presumably flavin) since this reaction, when conducted in heavy water, introduces deuterium at both the carbon atoms of the double bond.

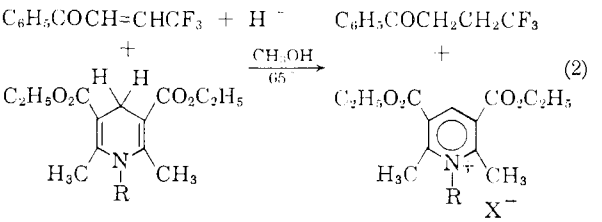
Many partially successful attempts have been made to produce model systems for the reduction of carbonyl compounds by dihydropyridines. The reduction of thioketones[13] with DPNH proceeds smoothly, and similar reactions show direct hydrogen transfer. The reduction of pyruvate has been achieved with a special N-alkyl dihydropyridine,[14] but the yields are low. Other photochemical[15] and non-photochemical[13,16] oxidation–reductions have been achieved; some are accompanied by direct hydrogen transfer, but most fall short in some respect; either the reduction occurs with poor yield, or uses an entirely unnatural substrate, or fails with an N-alkyl dihydropyridine (and therefore with true analogs of DPN and TPN).

Braude, Hannah and Linstead[17] carried out numerous reductions of the olefinic bond in maleic



(1)

acid, maleic anhydride, diethyl maleate, diethyl fumarate, etc., with the "Hantzsch compound," 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine. Similar reductions (see Experimental) readily occur at the olefinic bond of benzoylacrylic acid. The role of the carboxyl group in this reduction (or the role of the second carboxyl group in the reduction of maleic acid) was not understood; furthermore, these reductions had not been achieved with an N-alkyl dihydropyridine. To investigate these points, 1-phenyl-4,4,4-trifluoro-2-buten-1-one was synthesized, and submitted to reduction by dihydropyridines. These reductions (where R is



(2)

either a hydrogen atom or a methyl group) proceed readily in good yield and are accompanied by direct transfer of hydrogen from the reducing agent to the position beta to the carbonyl group. They thus parallel the enzymatic reduction achieved by McGuire and Tompkins.

Experimental[18]

1-Phenyl-3-hydroxy-4,4,4-trifluorobutan-1-one.—A mixture of 60.0 g. (0.50 mole) of acetophenone and 58.0 g. (0.50 mole) of trifluoroacetaldehyde hydrate (Columbia Organic Chemicals Co.) dissolved in 75.0 g. of acetic acid was heated at reflux for 98 hours. The cooled reaction mixture was poured into 3 l. of water, and extracted with chloroform. The combined chloroform extracts were dried over magnesium sulfate, and taken nearly to dryness on a rotary evaporator. This oil was dissolved in 200 ml. of petroleum ether (35–60°), and placed in a refrigerator overnight. The resulting white crystals were filtered, washed with three 30-ml. portions of cold petroleum ether, and dried. Evaporation and chilling of the combined washings and mother liquor yielded a second crop of pure material; yield 34.9 g. (32%), m.p. 78.5–79.5°, λ_{max}^{MeOH} 242 mμ (ε 12,500) and 281 mμ (ε 1,000); infrared 2.82(s), 5.92(s), 14.6(s) μ.

Anal. Calcd. for $C_{10}H_9O_2F_3$: C, 55.06; H, 4.16; F, 26.13. Found (H): C, 55.08; H, 4.20; F, 25.12.

(2) B. Vennesland and F. H. Westheimer, in "The Mechanism of Enzyme Action," McElroy and Glass, Eds., the Johns Hopkins Press, Baltimore, Md., 1954, p. 357.

(3) F. A. Loewus, P. Ofner, H. F. Fisher, F. H. Westheimer and B. Vennesland, *J. Biol. Chem.*, **202**, 699 (1953); F. A. Loewus, F. H. Westheimer and B. Vennesland, *J. Am. Chem. Soc.*, **75**, 5018 (1953).

(4) H. R. Levy and B. Vennesland, *J. Biol. Chem.*, **228**, 85 (1957), and references cited therein; T. Nakamoto and B. Vennesland, *ibid.*, **235**, 202 (1960); B. K. Stearns and B. Vennesland, *ibid.*, **235**, 205, 209 (1960).

(5) F. H. Westheimer, H. Fisher, E. E. Conn and B. Vennesland, *J. Am. Chem. Soc.*, **73**, 2403 (1951).

(6) M. Pullman, A. San Pietro and S. P. Colowick, *J. Biol. Chem.*, **206**, 129 (1954).

(7) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2261 (1955).

(8) R. F. Hutton and F. H. Westheimer, *Tetrahedron*, **3**, 73 (1958).

(9) W. Traber and P. Karrer, *Helv. Chim. Acta*, **41**, 2066 (1958).

(10) N. O. Kaplan in "The Enzymes," P. D. Boyer, H. Lardy and K. Myrback, Eds., Academic Press, Inc., New York, N. Y., 1960. Vol. III, p. 105.

(11) T. P. Singer and E. B. Kearney, *Adv. in Enzymol.*, **15**, 79 (1954).

(12) J. L. Graves and B. Vennesland, *J. Biol. Chem.*, **226**, 307 (1957).

(13) R. Abeles, R. F. Hutton and F. H. Westheimer, *J. Am. Chem. Soc.*, **79**, 712 (1957).

(14) K. Wallenfels and D. Hoffman, *Tetrahedron Letters*, **15**, 10 (1959); K. Wallenfels and M. Gelrich, *Ber.*, **92**, 1406 (1959).

(15) (a) J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, **77**, 447 (1955); (b) W. R. Frisell and C. G. Mackenzie, *Proc. Natl. Acad. Sci. (U. S.)*, **45**, 1568 (1959); (c) J. L. Kurz, R. Hutton and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 584 (1961).

(16) R. H. Abeles and F. H. Westheimer, *ibid.*, **80**, 5459 (1958); B. Kadis, Abs. of 135th Meeting of the American Chemical Society, Boston, Mass., 1959, p. 24; John L. Graves, unpublished.

(17) E. A. Braude, J. Hannah and R. Linstead, *J. Chem. Soc.*, 3249, 3257, 3268 (1960).

(18) All melting points are corrected Fisher block values unless otherwise indicated. Analyses are by Huffman Microanalytical Lab. (H) and Schwarzkopf Microanalytical Lab. (S).

1-Phenyl-4,4,4-trifluoro-2-buten-1-one.—The yellow solution of 22.9 g. (0.105 mole) of 1-phenyl-3-hydroxy-4,4,4-trifluorobutan-1-one in 212 g. of ice-cold concentrated sulfuric acid was allowed to stand overnight at room temperature; it was then poured into ice-water, and extracted with three 75-ml. portions of ether. The combined ether extracts were washed with water, dilute sodium bicarbonate, and saturated brine. The resulting ethereal solution was dried over magnesium sulfate, and evaporated to an oil. This oil was dissolved in a minimum of warm methanol (35°), taken just to the cloud point with water, cleared with methanol, and placed in a freezer overnight. The resulting crystals were filtered, washed once with 10 ml. of cold methanol, and dried at 0.25 mm. at room temperature. Further crops were obtained by careful work up of washings and mother liquors; yield 16.6 g. (79%), m.p. 29–29.5°, λ_{max}^{MeOH} 222 mμ (ε 7,610) and 265 mμ (ε 8,720); infrared, 5.91(s) and 14.6(s) μ.

Anal. Calcd. for $C_{10}H_7OF_3$: C, 60.00; H, 3.53; F, 28.48; mol. wt., 200.16. Found (S): C, 59.90; H, 3.13; F, 27.91; mol. wt. (benzene f.p.), 190.

1-Phenyl-4,4,4-trifluorobutan-1-one.—A solution of 2.00 g. (0.01 mole) of 1-phenyl-4,4,4-trifluoro-2-buten-1-one in a mixture of 50 ml. of petroleum ether (35–60°) and 5 ml. of dioxane was hydrogenated at atmospheric pressure and room temperature in 30 minutes over 0.0227 g. (0.1 mmole) of platinum(IV) oxide. After the uptake of hydrogen was complete, the filtered solution was reduced to a semi-solid at the rotary evaporator. This mixture, dissolved in a minimum of petroleum ether (35–60°), was chromatographed in that petroleum ether on a 20 × 200 mm. column of Woelm neutral alumina, grade III; yield 1.24 g. (62%), m.p. 59.8–60.8°, λ_{max}^{MeOH} 242 mμ (ε 11,500); infrared, 5.96(s), 14.5(s) μ.

Anal. Calcd. for $C_{10}H_9OF_3$: C, 59.40; H, 4.49; F, 28.19; mol. wt., 202.17. Found (S): C, 59.15; H, 4.53; F, 27.59; mol. wt. (Rast), 199.

The proton nuclear magnetic resonance (n.m.r.) spectrum showed a broad-band multiplet at[19] $\delta = -2.1$ to -2.8, assigned to the methylene group adjacent to the trifluoromethyl group, and split both by the fluorine atoms and the hydrogen atoms in the adjacent methylene group. Absorption centered at $\delta = -3.2$, corresponding to the methylene group adjacent to the carbonyl function, was split into an unsymmetrical triplet by the neighboring methylene group. The third absorption at $\delta = -7.5$ to -8.0 was assigned to the aromatic ring protons. The three peaks had an integrated intensity ratio of 5:2:2. The fluorine n.m.r. spectrum showed a symmetrical triplet at $\delta = +67.5$ from trichlorofluoromethane.

A red mono-2,4-dinitrophenylhydrazone[20] was obtained in analytical purity on recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{13}O_4N_4F_3$: C, 50.26; H, 3.43; F, 14.91. Found(H): C, 50.47; H, 3.69; F, 14.8.

1-Phenyl-3-methoxy-4,4,4-trifluorobutane-1-one.—A mixture of 2.0 g. (0.110 mole) of 1-phenyl-4,4,4-trifluoro-2-buten-1-one, one pellet of sodium hydroxide and 50 ml. of methanol was allowed to stand at room temperature for 24 hours. The resulting solution was reduced in volume, added to 10 ml. of water, and extracted with three 25-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, and evaporated to dryness. The resulting solid was sublimed to give sticky white crystals, and then recrystallized from petroleum ether (35–60°), yielding white blunt needles, m.p. 47.5–48.6°.

Anal. Calcd. for $C_{11}H_{11}O_2F_3$: C, 56.89; H, 4.78; F, 24.55. Found (S): C, 57.29; H, 4.85; F, 24.82.

***trans*-β-Benzoylacrylic Acid.**—Eastman Kodak Co. yellow label material was recrystallized four times from benzene to give pale yellow needles, m.p. 95.5–97° (reported 94–96°,[21] 96–97°[22]).

(19) All chemical shifts are measured in carbon tetrachloride solution with hexamethyldisiloxane as an internal standard, $\delta = 0$, unless otherwise specified.

(20) Obtained by the procedure in "The Systematic Identification of Organic Compounds," R. L. Shriner, R. C. Fuson and D. Y. Curtin, 4th Edition, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 219.

(21) *Org. Syntheses*, **29**, 11 (1949).

(22) H. von Pechmann, *Ber.*, **15**, 881 (1882).

β-Benzoylpropionic Acid.—Crude material (Harvard Research Stores) was recrystallized to constant melting point from benzene–ligroin, yielding white plates, m.p. 116.5–117.5° (reported 116°,[23] 117–118°[24]).

2,6-Dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine[25] after three recrystallizations from ethanol yielded greenish-yellow needles, m.p. (sealed evacuated capillary) 191.5–193°; λ_{max}^{MeOH} 369 mμ (ε 7,660), 229 mμ (ε 16,500), inflection 248 mμ (ε 9,060).

4,4-Dideuterio-2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine.—A mixture of 1.0 g. (0.031 mole) of granular polymeric Merck Limited formaldehyde-d_2, 0.023 g. (0.0001 mole) of *p*-toluenesulfonic acid and 10 ml. of water was heated at reflux until it was homogeneous (10 hours). To this solution, cooled and neutralized with ammonium hydroxide, was added 7.54 g. (0.058 mole) of ethyl acetoacetate and a solution of 0.54 g. (0.032 mole) of concentrated ammonia in 3 g. of ethanol. After 5 days at room temperature, 4.8 g. (57%) of pale greenish-yellow crystals was obtained, m.p. 191.2–192.4° (sealed evacuated capillary).

2,6-Dimethyl-3,5-dicarboethoxypyridine.—To a solution of 1.00 g. (0.0039 mole) of 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine in 150 ml. of benzene and 70 ml. of ether was added a warm (40°) solution of 0.584 g. (0.002 mole) of potassium dichromate (finely ground) in 130 ml. of glacial acetic acid, 5 ml. of benzene and the minimum amount of water necessary for solution (about 25 drops). This solution was allowed to stand for 7 minutes (during which time a dark green color rapidly developed), cooled, and neutralized with 6–10 *M* sodium hydroxide solution. The mixture was extracted with three 100-ml. portions of ether. The ether layers were combined, reduced in volume, dried over magnesium sulfate, and taken to dryness. Recrystallization of the resulting white crystals from methanol–water yielded 0.894 g. (89.4%) of long white needles, m.p. 72.0–72.5°; reported (from other methods of oxidation) 72°[26]; 73°.[27]

1,2,6-Trimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine on crystallization from ethanol gave yellow needles, m.p. (s.e.c.) 105–106°, reported[15c] 105–106°; λ_{max}^{MeOH} 232 mμ (ε 14,500), 263 mμ (ε 9,030), 352 mμ (ε 6,480).

1,2,6-Trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine.—1,2,6-Trimethyl-3,5-dicarboethoxypyridinium monomethylsulfate[28] was obtained as a yellow sirup from 0.894 g. (0.0036 mole) of 2,6-dimethyl-3,5-dicarboethoxypyridine. It was dissolved in a minimum of water, filtered, and added to a solution of 1.06 g. (0.010 mole) of sodium carbonate and 1.74 g. (0.010 mole) of sodium dithionite (80%) in 40 ml. of water at 50–55°. The resulting opaque yellow solution was shaken for 30 minutes, allowed to cool, and filtered. The crystals thus obtained were recrystallized from ethanol–water, yielding 0.782 g. (76.6%), m.p. 85.8–86.9° (uncorrected sealed evacuated capillary); reported 86–87°,[27] 88°.[15c]

The proposed structure was confirmed by the proton n.m.r. spectrum, determined with a Varian A-60 spectrometer. The ethyl groups gave rise to the typical triplet centered at $\delta = -1.22$ and quartet centered at $\delta = -4.06$, with $J = 7$ c.p.s. The peak at $\delta = -3.08$ corresponded to the N-methyl group, a peak at -2.28 to the two C-methyl groups and a relatively broad peak at $\delta = -2.97$ to the two protons in the 4-position. With higher resolution, the peak at $\delta = -2.28$ was resolved into a tight triplet, with $J = 1$ c.p.s., corresponding to splitting of the signals from the C-methyl groups by the allylic hydrogen atoms in the 4-position. The broad peak at -2.97 was not resolved.

4,4-Dideuterio-1,2,6-trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine.—The dideuterio-N-methyl Hantzsch compound was synthesized in 75% yield from 4,4-dideuterio-2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine *via* the monomethylsulfate in the same manner as described for the non-isotopic material, except that deuterium oxide replaced water in the reduction. The physical properties of the

(23) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 81.

(24) J. Sudborough, *J. Chem. Soc.*, 1227 (1912).

(25) H. Meyer and H. Tropsch, *Monatsh.*, **35**, 207 (1914).

(26) P. Griess and G. Harrow, *Ber.*, **21**, 2740 (1888).

(27) I. Guareschi and E. Grande, *Chem. Zentr.*, **70**, II, 440 (1899); F. Engelmann, *Ann.*, **231**, 37 (1885).

(28) O. Mumm and J. Diedericks, *ibid.*, **538**, 195 (1939); P. R. Brooks and P. Karrer, *ibid.*, **605**, 1 (1957).

product were the same as those of the non-deuterated compound, but the n.m.r. spectrum was significantly changed; no peak was observed at $\delta = -2.97$, and under high resolution the peak at $\delta = -2.28$ could not be resolved.

Exchange Experiments. (A) **β,β-Dideuterio-β-benzoylpropionic Acid.**—A mixture of 0.499 g. (2.8 mmoles) of β-benzoylpropionic acid, 0.122 g. (3.27 mmoles) of sodium hydroxide and 5.0 ml. of deuterium oxide was heated for 70 min. at 25°, acidified with a few drops of concentrated hydrochloric acid, and filtered. The precipitated acid was washed with water and dried at 1 mm. over potassium hydroxide.

Deuterium was removed from the carboxyl group by dissolving the acid in 2 ml. of acetone and reprecipitating with 4 ml. of water. After repeating this process, the dried product was analyzed for deuterium by combustion and mass spectroscopy.

(B).—A solution of 0.007 g. (0.039 mmole) of β,β-dideuterio-β-benzoylpropionic acid in 0.14 ml. of 0.381 *M* aqueous sodium hydroxide was allowed to stand for 490 min. at 25°. The solution was then acidified with hydrochloric acid, filtered, washed, dried at 1 mm. over potassium hydroxide, and the product subjected to a mass spectrographic analysis for deuterium. None was found.

(C) **1-Phenyl-2,2-dideuterio-4,4,4-trifluorobutan-1-one.**—A heterogeneous mixture of 0.500 g. (2.5 mmoles) of 1-phenyl-4,4,4-trifluorobutan-1-one and 0.200 g. of sodium hydroxide in 5 ml. of ether and 5 ml. of deuterium oxide was heated at reflux for 20 minutes, then taken to dryness on a rotary evaporator. The resulting slurry was recharged with 5 ml. of ether and 5 ml. of deuterium oxide, refluxed, and evaporated. The procedure was carried out five times. The final solution was extracted with three 5-ml. portions of ether, and the deuterated ketone purified by vacuum sublimation.

The proton n.m.r. spectrum of the product showed a quartet centered at $\delta = -2.4$, corresponding to the methylene group adjacent to and split by the trifluoromethyl group. The only other absorption was a large peak centered at $\delta = -7.6$, assigned to the aromatic ring protons. The integrated intensity ratios of these two peaks correspond to 5:2. No absorption occurred near $\delta = -3.1$, where the methylene group adjacent to the carbonyl absorbs in the non-isotopic ketone.

Mass Spectrometric Deuterium Analyses.—Samples were burned in a combustion train, and the water collected. The water was converted to hydrogen over hot zinc, and the HD–H_2 ratio determined with the mass spectrometer. Samples containing excess deuterium were always diluted with unlabeled material such that measured deuterium to hydrogen ratios were approximately 0.004. They were combusted and converted to deuterium gas by the methods described in detail by Fry,[29] and analyzed with a Consolidated–Nier isotope ratio mass spectrometer, model 21–201.

Hydrogen Transfer Experiments. (A) **With 2,6-Dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine.**—A mixture of 0.5136 g. (0.002 mole) of 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine and 0.4030 g. (0.002 mole) of 1-phenyl-4,4,4-trifluoro-2-buten-1-one in 20 ml. of methanol was refluxed for 25 hours, evaporated to dryness, and chromatographed in petroleum ether (35–60°) on a 24 × 120 mm. column of Woelm neutral alumina, grade III, using petroleum ether (35–60°), benzene, and ether in a graded series of eluents. 1-Phenyl-4,4,4-trifluorobutan-1-one (83.5% yield) was shown to be identical to the synthesized saturated ketone by m.m.p. (50/50 and 75/25 w./w. proportion), by infrared and by n.m.r. spectroscopy. The expected 2,6-dimethyl-3,5-dicarboethoxy pyridine was isolated in the 50% benzene–ether fraction in 98.9% yield.

A mixture of 0.507 g. (0.002 mole) of 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine and 0.353 g. (0.002 mole) of β-benzoylacrylic acid was refluxed in 20 ml. of methanol for 24 hours, cooled, and taken to dryness at room temperature. The residue, taken up in ether, was extracted with aqueous potassium carbonate, and the aqueous extracts combined.

Acidification of aqueous extracts with hydrochloric acid produced 0.218 g. (61.2%) of β-benzoylpropionic acid, m.p. 116.3–117.5°, m.m.p. 116.3–117.4° with authentic material.

Evaporation of the solvent from the dried organic layer, and recrystallization of the solid residue from ethanol–water gave 0.354 g. (70.5%) of 2,6-dimethyl-3,5-dicarboethoxypyridine, m.p. 71.6–72.3°, m.m.p. 71.7–72.3° with authentic material.

(B) **With 1,2,6-Trimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine.**—A mixture of 0.071 g. (0.315 mmole) of 1,2,6-trimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine, 0.062 g. (0.309 mmole) of 1-phenyl-4,4,4-trifluoro-2-buten-1-one and 0.100 g. (0.603 mmole) of freshly prepared pyridinium perchlorate[30] (to prevent the reaction mixture from becoming basic during the course of the hydrogen transfer, and thus destroying the pyridinium salt formed) in 20 ml. of methanol was refluxed for 48 hours, cooled, and taken to dryness on the rotary evaporator.

The product was transferred with petroleum ether to a column of Woelm neutral alumina, grade III, eluted with more petroleum ether, and 7-ml. fractions collected. Fractions 8–11 yielded 0.029 g. (46.5%) of 1-phenyl-4,4,4-trifluorobutan-1-one, m.p. 58.8–59.6° (after sublimation) mixed m.p. not depressed (in 50/50 and 75/25 w./w. proportions) by authentic material.

In another reaction (carried out with limiting pyridinium perchlorate) a mixture of 0.670 g. (2.97 mmoles) of 1,2,6-trimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine, 0.700 g. (3.50 mmoles) of 1-phenyl-4,4,4-trifluoro-2-buten-1-one and 0.350 g. (2.11 mmoles) of freshly prepared pyridinium perchlorate in 50 ml. of methanol was heated at reflux for 24 hours, reduced to 15-ml. volume, added to 50 ml. of water, and separated into an aqueous layer and an ether layer.

After exhaustive extraction with ether, the light yellow aqueous solution was taken to dryness on a rotary evaporator, and yielded 0.2625 g. (39%) of crude 1,2,6-trimethyl-3,5-dicarbomethoxypyridinium perchlorate. A portion of this recrystallized from methanol yielded an infrared spectrum, m.p. and m.m.p. identical to that of an authentic sample.[15c]

The ethereal solution, washed with dilute hydrochloric acid, dilute sodium hydroxide, saturated sodium chloride, dried over magnesium sulfate, and taken to dryness, yielded on chromatography as described above 0.2789 g. (69%) of 1-phenyl-4,4,4-trifluorobutan-1-one.

Deuterium Transfer Experiments. (A) **β-Benzoylpropionic Acid.**—A solution of 0.256 g. (0.001 mole) of 4,4-dideuterio-2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine and 0.177 g. (0.001 mole) of β-benzoylacrylic acid in 10 ml. of methanol was heated at reflux for 39 hours. After the usual work up, 0.068 g. (38%) of 2-benzoylpropionic acid, m.p. and m.m.p. with authentic material 116.7–117.5°, was isolated. A duplicate run yielded 0.065 g. A 0.027-g. sample of this deuterated material was dissolved in 0.53 ml. of 0.381 *M* sodium hydroxide and allowed to stand for 490 min. at 25° before it was precipitated with hydrochloric acid, collected, washed, and dried over potassium hydroxide at 1 mm.

The results of the deuterium analyses for the β-benzoylpropionic acid are summarized in Table I. The number of

TABLE I

RESULTS OF DEUTERIUM ANALYSES

Sample	(D^{18}/H)	Dilution factor	H or D sites	Atoms D, found	Average atoms D
Hantzsch-4,4-d_2	0.00392			1.95	
(starting material)	.00388	26.26	19	1.93	1.94
BPA[a] deuterium	.00381			0.951	
transfer prod.	.00375	25.03	10	.934	0.942
	.00378			.941	
BPA[a] exchange run	.00371			1.87	
A	.00373			1.88	
	.00370	50.61	10	1.87	1.87
	.00370			1.87	
BPA[a] exchange run	.00017			0.010	
B	.00018	5.90	10	.011	0.011
BPA[a]	.00369			.927	
D expt. treated	.00373	25.20	10	.937	0.937
with H_2O/OH^-	.00378			.948	

[a] Benzoylpropionic acid.

(29) K. T. Fry, Jr., Thesis, Harvard University, 1960.

(30) F. Arndt and P. Nachtwey, *Ber.*, **59**, 446 (1926).

deuterium atoms per molecule of a particular sample may be calculated by using the equation

$$\text{atoms D} = \left[\frac{1}{\frac{1}{(D^{xs}/H)} + 1}\right]\left[\begin{matrix}\text{dilution}\\ \text{factor}\end{matrix}\right]\left[\begin{matrix}\text{number of H or D}\\ \text{sites per molecule}\end{matrix}\right]$$

where (D^{xs}/H) is the ratio measured for diluted material, and the "dilution factor" is given by the expression

$$\text{dilution factor} = \frac{[\text{moles labeled cmpd.}] + [\text{moles ordinary cmpd.}]}{[\text{moles labeled cmpd.}]}$$

The results of these combustion experiments were confirmed with n.m.r. spectra.

Proton n.m.r. spectra of the sodium salts of both authentic β-benzoylpropionic acid and the acid derived from the deuterium transfer experiment in deuterium oxide 0.1 *M* in sodium deuteroxide gave identical patterns at 60 mc. for the aromatic hydrogens at $\delta = -3.2$ to -2.4 (Roberts scale, $\delta_{H_2O} = 0$). The only other absorption in either case consisted of a single unsplit line at $\delta = +2.4$. Crude estimates of the peak areas gave aromatic protons/methylene proton(s) ratios of 5:2 and 5:1 for the normal and the deuterium transfer product, respectively.

(B) **1-Phenyl-4,4,4-trifluorobutan-1-one.**—The majority of the determinations of deuterium in benzoylpropionic acid was by combustion; with the exception of one experiment (for confirmation) the deuteration of 1-phenyl-4,4,4-trifluorobutan-1-one was estimated by proton and fluorine n.m.r. spectra.

A solution of 0.192 g. (0.75 mmole) of 4,4-dideuterio-2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine, 0.300 g. (1.50 mmoles) of 1-phenyl-4,4,4-trifluoro-2-buten-1-one and 0.406 g. (2.26 mmoles) of pyridinium perchlorate in 40 ml. of methanol was refluxed for 24 hours. After the usual work-up, 0.032 g. (20%) of product was obtained, m.p. 57.3–59.0°, m.m.p. with authentic 1-phenyl-4,4,4-trifluorobutan-1-one, 57.6–59.0°. Proton n.m.r. of this compound demonstrated multiple absorption at $\delta = -7.63$, characteristic of the phenyl protons; a doublet centered at $\delta = -3.14$, assigned to the methylene group adjacent to the carbonyl, split by *one* neighboring hydrogen; and a low intensity diffuse multiplet centered at $\delta = -2.5$. The integrated intensities were 5:2:1. The fluorine n.m.r. showed a doublet at $\delta = +68.3$ from trichlorofluoromethane, showing that only one hydrogen atom was attached to the adjacent carbon atom.

Anal. Calcd. for $C_{10}H_8DOF_3$: Atom % D, 11.1. Found[31]: Atom % D, 10.35.

In a similar way, 0.211 g. (0.745 mmole) of 4,4-dideuterio-1,2,6-trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine, 0.300 g. (1.50 mmoles) of 1-phenyl-4,4,4-trifluoro-2-buten-1-one and 0.406 g. (2.26 mmoles) of pyridinium perchlorate in 40 ml. of methanol were heated at reflux for 48 hours. After the usual work-up 0.030 g. (20%) product was isolated; m.p. and m.m.p. with authentic 1-phenyl-4,4,4-trifluoro-butan-1-one was 59.0–59.8°, The proton and fluorine n.m.r. demonstrated the presence of only one hydrogen atom on the carbon atom beta to the carbonyl group.

Results

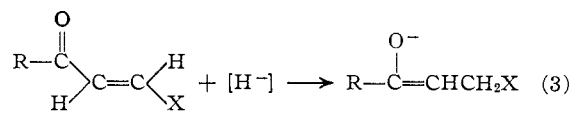
In summary, the reactions shown in eq. 1 and 2 proceed in good yield near neutrality in boiling methanol, or under comparable conditions. The reduction of β-benzoylacrylic acid has been achieved with the Hantzsch compound, 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine. When the dideuterio analog of the Hantzsch compound was used as the reducing agent, a deuterium atom from the reduced pyridine was introduced onto the carbon atom beta to the ketonic carbonyl group. This fact was established by showing that no deuterium was lost from the monodeuterio-β-benzoylpropionic acid when it was allowed to stand in alkaline solution, although control experiments demonstrated that the two hydrogen atoms adjacent to the ketonic carbonyl group were readily exchanged under these same experimental conditions.

The reduction of 1-phenyl-4,4,4-trifluoro-2-buten-1-one has been achieved both with the Hantzsch compound and with its N-methyl derivative. The latter is oxidized to an N-methylpyridinium salt; in this respect, the reduction parallels those where DPNH and TPNH are oxidized to DPN and TPN. Again, when the 4,4-dideuterio analogs of the Hantzsch compound and of the N-methyl Hantzsch compound were used as reducing agents, one atom of deuterium per molecule was introduced into the resulting 1-phenyl-4,4,4-trifluorobutan-1-one. Both the composition and the structure of the monodeuterated ketone were demonstrated by n.m.r. spectra; one deuterium atom was introduced into the position beta to the carbonyl group. The conclusion follows from the facts that the fluorine resonance of 1-phenyl-4,4,4-trifluorobutan-1-one was split into a triplet by the two hydrogen atoms of the adjacent methylene group, whereas in the deuterated reduction product, the fluorine resonance consisted of a clean doublet. The proton n.m.r. spectra confirmed the fact of deuteration, and the structure of the product; both the integrated intensities of the peaks and the splittings were consistent with the assignment of 1-phenyl-3-deuterio-4,4,4-trifluorobutan-1-one as the reaction product.

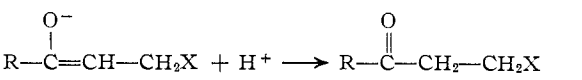
Discussion

The model system here reported resembles the enzymatic one achieved by McGuire and Tompkins[1] for the reduction of androstenedione to androstanedione. In both examples, an N-alkyl dihydropyridine presumably reduces the carbon–carbon double bond of an α,β-unsaturated ketone; in both examples, a hydrogen atom is transferred from the reducing agent to the position beta to the ketonic carbonyl group. (The possible qualifications of this conclusion for the enzymatic synthesis were discussed in the Introduction.)

The mechanism of the non-enzymatic reduction (and by inference of the enzymatic one) cannot be stated with certainty. The reduction has so far been achieved only with α,β-unsaturated carbonyl compounds[17] and only with those properly substituted on the double bond. Since a trifluoromethyl group promotes the reaction as strongly as does a carboxyl group, the role of the second substituent is presumably electrostatic. The evidence therefore suggests that, in this model system, reduction occurs by transfer of a hydride ion from the dihydropyridine to the substrate, to form an enolate ion, followed by a rapid reaction of the enolate ion with a proton donor to yield the saturated ketone. However, reactions



(3)



(4)

(31) Analysis by J. Nemeth, 303 W. Washington St., Urbana, Ill.

which proceed by way of free-radical intermediates are also subject to polar influences.[32] Without further data, such as reaction kinetics and salt and solvent effects on the rate of reaction, a radical pathway involving transfer of a hydrogen atom cannot be eliminated at this time. Regardless of the details of mechanism, the model system has apparently led to satisfactory reaction by substituting an electrostatic acceleration by a trifluoromethyl group or a carboxyl group for the catalysis by the enzyme.

Unfortunately, the available examples of the model system are few. Several attempts to extend the generality of the reaction failed. A number of other dihydropyridines were tried without success; the list includes N-benzyldihydronicotinamide, 3,5-dicarboethoxy-1,4-dihydropyridine, 3-cyano-N-methyl-1,4-dihydropyridine, 3-cyano-N-phenyl-1,4-dihydropyridine, N-phenyldihydronicotinamide, N-benzyl-3,5-dicarboxamyl-1,4-dihydropyridine. The sharp requirements with respect to the structure of those ketones which can be reduced has already been mentioned. These restrictions probably arise because of the limitations in experimental conditions which are imposed upon the reduction. The reaction cannot be conducted except in slightly acid or neutral solution, since the trifluoromethyl olefin is extraordinarily sensitive to Michael addition. In the presence of an acetic acid–sodium acetate buffer, or even of a methoxyacetate–methoxyacetic acid buffer, the Michael addition of methanol to the double bond takes precedence over reduction; the successful experiments were carried out in the presence of added methoxyacetic acid or pyridinium perchlorate. (In mildly alkaline solution, N-alkyl pyridinium salts are also unstable.) On the other hand, strongly acid conditions (or in some cases even mildly acid conditions) are not tolerated by the notoriously acid-sensitive dihydropyridines. Presumably in enzyme systems, the protein can catalyze the reaction sufficiently to allow reduction even under very mild conditions, where the dihydropyridines are stable.

(32) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 384.

Acknowledgments.—The authors take pleasure in acknowledging a grant (N.I.H. 8486) from the National Institutes of Health which enabled us to carry out this investigation. P.E.K. wishes further to acknowledge his support from a Postdoctoral Fellowship awarded to him by the National Science Foundation. The authors also wish to express their indebtedness to Dr. John L. Graves, who carried out some of the preliminary experiments on the reduction of benzoylacrylic acid.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

Electrolytic Reduction of Cyclooctatetraene

BY THOMAS J. KATZ, WILLIAM H. REINMUTH AND DONALD E. SMITH

RECEIVED JULY 6, 1961

The electrolytic reduction of cyclooctatetraene in 96% dioxane–water is shown by oscillopolarography to proceed by reversible addition of two electrons to the hydrocarbon followed by an irreversible pseudo-first-order reaction of the resulting dianion with the solvent. The kinetics of the latter reaction are determined. The observed behavior supports the conclusions based on e.s.r. and n.m.r. studies that the geometries of the cyclooctatetraenyl anions are similar and unlike that of the hydrocarbon. The significance of the observed half-wave potential is discussed in terms of the compressional energy required to aromatize the cyclooctatetraene molecule and the energy level of the hydrocarbon m.o. being filled. It is concluded that this m.o. is non-bonding, consistent with a regular octagonal geometry for the cyclooctatetraenyl dianion.

Introduction

The high degree of stabilization due to π-electron delocalization which is characteristic of carbocyclic aromatic systems and which had been sought but found absent in the hydrocarbon cyclooctatetraene is to be found in the cyclooctatetraenyl anions.[1] Since the available observations[2] concerning the electrolytic reduction of cyclooctatetraene had suggested this hypothesis to us before our own experiments were begun, we submitted the polarographic behavior of cyclooctatetraene to further scrutiny. The results of this study, which are elaborated below, bear out the hypothesis and further confirm the conclusions derived by means of proton nuclear magnetic and electron spin resonance techniques.

(1) T. J. Katz, *J. Am. Chem. Soc.*, **82**, 3784 (1960); **82**, 3785 (1960); T. J. Katz and H. L. Strauss, *J. Chem. Phys.*, **32**, 1973 (1960).

(2) (a) R. M. Elofson, *Anal. Chem.*, **21**, 917 (1949); (b) J. H. Glover and H. W. Hodgson, *Analyst*, **77**, 473 (1952); (c) L. E. Craig, R. M. Elofson and I. J. Kessa, *J. Am. Chem. Soc.*, **75**, 480 (1953).

Mechanism of Aromatic Hydrocarbon Reductions

As a result of extensive investigation,[3-5] the mechanisms of the electrode reactions of a number of unsaturated hydrocarbons have come to be recognized, and some of their essential features are briefly stated. (1) Electron transfer occurs between the electrode and the first unfilled molecular orbital of the unsaturated hydrocarbon molecule.[6-8] (2) Electronic repulsion results in a decrease in the facility with which a second electron transfer occurs.[8,9] (3) Solvation and ion pairing

(3) G. J. Hoijtink, J. Van Schooten, E. de Boer and W. I. Aalbersberg, *Rec. trav. chim.*, **73**, 355 (1954).

(4) (a) H. A. Laitinen and S. Wawzonek, *J. Am. Chem. Soc.*, **64**, 1765 (1942); (b) S. Wawzonek and H. A. Laitinen, *ibid.*, **64**, 2365 (1942); (c) S. Wawzonek and J. W. Fan, *ibid.*, **68**, 2541 (1946).

(5) I. Bergman, *Trans. Faraday Soc.*, **50**, 829 (1954).

(6) A. Maccoll, *Nature*, **163**, 178 (1949).

(7) A. Pullman, B. Pullman and G. Berthier, *Bull. soc. chim. France*, 591 (1950).

(8) G. J. Hoijtink, *Rec. trav. chim.*, **74**, 1525 (1955).

(9) N. S. Hush and J. Blackledge, *J. Chem. Phys.*, **23**, 514 (1955).