chloride and the resulting mixture was allowed to stand at room temperature for 2 days and then diluted with 100 ml of ether. The ethereal solution was washed with water, 10% HCl, 10% Na_2CO_3, and water, dried (Na_2SO_4), and concentrated to give 7 g (96%) of a brown oil.

Isolation of (−)-*trans*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (3).—This amide was obtained by crystallization of the crude mixture of diastereomers from a concentrated hexane solution at Dry Ice–isopropyl alcohol bath temperature. The amide was collected by filtration and washed with cold hexane but melted upon warming to room temperature. This material was recrystallized six times at refrigerator temperature to give a viscous oil (at room temperature): $[\alpha]_D$ −14° (*c* 5, chloroform); ir (neat) 2.92 (N–H), 6.00 μ (C=O). The nmr spectrum indicated the presence of only one diastereomer.

Isolation of (+)-*trans*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (4).—This diastereomer was isolated by column chromatography of the residual amide mixture remaining after the isolation of **3**. Typically, 4 g of the oil mixture was chromatographed on 125 g of neutral alumina (Merck), eluting with petroleum ether followed by increasing concentrations of benzene–petroleum ether mixtures. The eluted oil was collected in approximately 200-mg portions and analyzed by nmr spectroscopy. The desired diastereomer **4** eluted first and the pure fractions from several columns were combined and crystallized from hexane to give colorless crystals: mp 70.5–71.5°; $[\alpha]_D$ −73° (*c* 5, chloroform). The nmr spectrum indicated the presence of only one diastereomer.

Anal. Calcd for $C_{24}H_{36}NO_2Br$: C, 63.99; H, 8.06; H, 3.11. Found: C, 63.72; H, 8.03; N, 3.15.

Synthesis of the Mixture of Diastereomers 5 and 6.—The mixture of diastereomeric amides was obtained as an oil in a 98% yield from the reaction of **2** with (−)-menthoxyacetyl chloride in pyridine as described for the synthesis of **3** and **4**.

Isolation of (+)-*cis*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (5).—This diastereomer was obtained by fractional crystallization of the crude amide mixture in hexane at refrigerator temperature to give colorless crystals: mp 121–122.5°; $[\alpha]_D$ +86° (*c* 5, methanol); ir (Nujol) 2.94 (N-H), 5.99 μ (C=O). The nmr spectrum indicated the presence of only one diastereomer.

Anal. Calcd for $C_{24}H_{36}NO_2Br$: C, 63.99; H, 8.06; N, 3.11. Found: C, 64.06; H, 8.08; N, 3.08.

Isolation of (−)-*cis*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (6).—The residual amide mixture remaining after the isolation of **5** was crystallized from hexane at Dry Ice–isopropyl alcohol bath temperature and the crude solid was recrystallized from hexane by slow evaporation of solvent at room temperature. The fine needle crystals which formed recrystallized from hexane: mp 104.5–105.5°; $[\alpha]_D$ −174° (*c* 4, methanol). The nmr spectrum indicated the presence of only one diastereomer.

(−)-*trans*-2-(*o*-Bromophenyl)cyclohexylamine.—To a solution of 0.45 g of **3** in 8 ml of glacial acetic acid was added 5 ml of concentrated HCl and the resulting solution was heated in a 105° oil bath for 40 hr, cooled, and diluted with 30 ml of water. This solution was extracted with three 25-ml portions of ether and then carefully basified to pH 11 with 50% NaOH, while cooling in an ice bath. The resulting cloudy solution was extracted with 100 ml of ether in three portions and the ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give 0.23 g (91%) of a yellow oil, $[\alpha]_D$ −56° (*c* 2, methanol). The ir and nmr spectra were identical with those of **1**. The hydrochloride salt was prepared as for **1**: mp 217–219°; $[\alpha]_D$ −46° (*c* 5, methanol).

(+)-*trans*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained upon an identical acidic hydrolysis of **4**, $[\alpha]_D$ +56° (*c* 2, methanol). The hydrochloride salt was prepared as for **1**: mp 217–219°; $[\alpha]_D$ +46° (*c* 4, methanol).

(+)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained as an oil upon an acidic hydrolysis of **5**, as previously described for the hydrolysis of **3**, $[\alpha]_D$ +109° (*c* 3, methanol). The ir and nmr spectra were identical with those of **2**. The hydrochloride salt was prepared as for **2**: mp 240–242°, sublimes extensively; $[\alpha]_D$ +123° (*c* 4, methanol).

(−)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained as an oil upon the acidic hydrolysis of **6**, $[\alpha]_D$ −110° (*c* 2, methanol). The hydrochloride salt was prepared as for **2**: mp 240–242°, sublimes extensively; $[\alpha]_D$ −122° (*c* 4, methanol).

Registry No.—**1**, 30808-81-2; **1** HCl, 30808-95-8; **2**, 30808-82-3; **2** HCl, 30808-96-9; **3**, 30808-83-4; **4**, 30808-84-5; **5**, 30808-85-6; **6**, 30808-86-7; *trans*-4-nitro-5-(*o*-bromophenyl)cyclohexene, 30808-87-8; *trans*-2-(*o*-bromophenyl)nitrocyclohexane, 30808-88-9; *cis*-2-(*o*-bromophenyl)nitrocyclohexane, 30896-88-9; (−)-*trans*-2-(*o*-bromophenyl)cyclohexylamine, 30808-89-0, 30808-93-6 (HCl); (+)-*trans*-2-(*o*-bromophenyl)cyclohexylamine, 30808-90-3, 30808-97-0 (HCl); (+)-*cis*-2-(*o*-bromophenyl)cyclohexylamine, 30808-91-4, 30808-98-1 (HCl); (−)-*cis*-2-(*o*-bromophenyl)cyclohexylamine, 30808-92-5, 30808-94-7 (HCl).

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The Mechanism of the Base-Catalyzed Conversion of Nitriles to Amides by Hydrogen Peroxide

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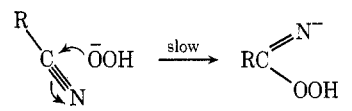
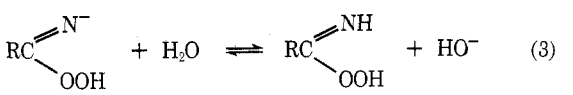
The conversion of nitriles to amides by alkaline solutions of hydrogen peroxide is a well-known preparative procedure.[1] Wiberg[2] has investigated the mechanism of this reaction in the pH range 7–8. Our interest in the nucleophilic reactivity of peroxy anions[3] and the α effect[4] led us to a reinvestigation of this reaction. Wiberg's mechanism,[2] eq 2–4, involves rate-

$$RC{\equiv}N + 2\,H_2O_2 \xrightarrow{HO^-} RC(=O)NH_2 + O_2 + H_2O \qquad (1)$$



(2)



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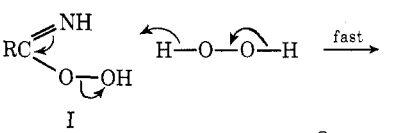
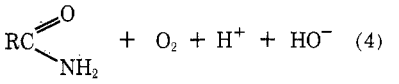




(4)

(1) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 469.

(2) K. B. Wiberg, *J. Amer. Chem. Soc.*, **75**, 3961 (1953); K. B. Wiberg, *ibid.*, **77**, 2519 (1955).

(3) J. E. McIsaac, Jr., H. A. Mulhausen, and E. J. Behrman, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, ORGN 70.

(4) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

determining nucleophilic attack of the anion of hydrogen peroxide on the nitrile carbon followed by a rapid reaction of the intermediate peroxycarboximidic acid I with hydrogen peroxide.

In order to obtain rate data for eq 2 in aqueous solution, we chose to study the reaction using *p*-cyanobenzoic acid as the substrate. We were, however, unable to obtain satisfactorily reproducible kinetics for the reaction in carbonate buffers. EDTA (ethylenediaminetetraacetic acid) was added as a sequestering agent to suppress metal ion catalyzed decomposition of hydrogen peroxide. Representative data under pseudo-first-order conditions in the region of pH 10 are given in Table I. Rate data were also obtained under second-order conditions in 0.5 M NaOH and 8.5×10^{-5} M EDTA by following the production of oxygen. These experiments confirmed the stoichiometry of eq 1 with respect to oxygen and yielded rate constants of approximately 1 M^{-1} min^{-1} in rough agreement with the data of Table I. However, both second-order and first-order plots exhibited significant curvature.

TABLE I

KINETIC DATA FOR THE REACTION OF HYDROGEN PEROXIDE AND *p*-CYANOBENZOIC ACID AT 25° [a]

pH	[Nitrile], M	$t_{1/2}$, min	k_{HOO^-}, M^{-1} min^{-1} [b]
9.79	2.5×10^{-2}	200	1.35
10.00	5.0×10^{-2}	102	0.82
10.00	5.0×10^{-2}	71	1.15
10.07	2.5×10^{-2}	162	0.90

[a] Initial $[H_2O_2] = 2 \times 10^{-3}$ M. Carbonate buffers contained 8.5×10^{-5} M EDTA; $\mu = 1.0$ M with KCl in deionized water. [b] Calculated using a pK_a for H_2O_2 of 11.37[3] and statistically and stoichiometrically corrected.

These data and the well-documented susceptibility of peroxide reactions to metal ion catalysis led us to carry out a series of kinetic experiments in carbonate buffers in which all solutions were prepared from the same bottles in order to evaluate the effects of EDTA. Figure 1 demonstrates that in the presence of EDTA, hydrogen peroxide alone is stable but that it disappears rapidly in the presence of the nitrile. In the absence of EDTA, the disappearance of hydrogen peroxide is roughly five times faster when the nitrile is present. This figure also shows the complex kinetics by the evident curvature of the plots. A study of the effects of EDTA concentration indicates that EDTA itself, or its complexes with metal ions, is involved in reaction with some species in solution (perhaps the intermediate peroxycarboximidic acid).

In phosphate buffers, however, EDTA has no observable effect, perhaps because phosphates themselves are good sequestering agents. In agreement with Wiberg,[2] we find that under these conditions second-order plots are linear and show no evidence of metal ion involvement. At 50° and pH 6.77 in 0.1 M phosphate buffer we find $k_{HOO^-} = 4.1 \times 10^1$ M^{-1} min^{-1};[5] this compares with Wiberg's[2] value of $k_{HOO^-} = 4.4 \times 10^2$ M^{-1} min^{-1} for benzonitrile in 50% acetone–water. The addition of allyl acetate to the system in phosphate buffer halves the rate of loss of hydrogen peroxide;

(5) Initial $[H_2O_2] = 0.1$ M, initial [nitrile] $= 5.0 \times 10^{-2}$ M; in the presence of 1×10^{-3} M EDTA; calculated using a pK_a for H_2O_2 at 50° of 10.98.[3]

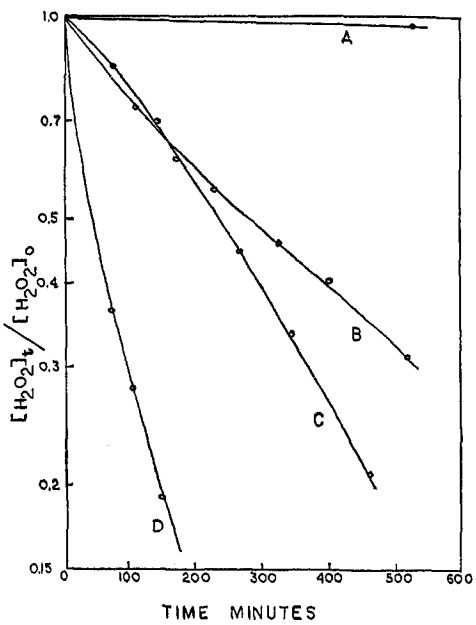


Figure 1.—First-order plots demonstrating the effect of EDTA and *p*-cyanobenzoic acid on the rate of loss of H_2O_2. Initial $[H_2O_2] = 3.5 \times 10^{-3}$ M in 0.3 M carbonate buffer at pH 9.75; $\mu = 1.0$ with KCl; $T = 25°$. A, [EDTA] $= 8.5 \times 10^{-5}$ M, no nitrile; B, no EDTA, no nitrile; C, [EDTA] $= 8.5 \times 10^{-5}$ M, [nitrile] $= 2.5 \times 10^{-2}$ M; D, [nitrile] $= 2.5 \times 10^{-2}$ M, no EDTA.

this is expected on the basis of the work of Payne[6] and his colleagues on the epoxidation of olefins by peroxycarboximidic acids.

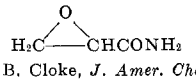
We conclude that Wiberg's[2] mechanism is substantially correct for the system he investigated, but at higher pH under the usual preparative conditions,[1] in the absence of EDTA or phosphates, there can be a significant contribution to the rate of loss of hydrogen peroxide by a metal-catalyzed free-radical reaction.[7]

As a test for the proposed mechanism[2] of the fast step, eq 4, we have carried out a double-isotope-labeling experiment[9] at pH 7.4. Wiberg's mechanism predicts that for doubly labeled hydrogen peroxide H–^{18}O–^{18}O–H, 100% of the double label will be retained, appearing as $^{36}O_2$ (no scrambling). An experiment was performed in which 16% of the hydrogen peroxide was doubly labeled; 81% of the original double label appeared as $^{36}O_2$ in the product oxygen. The data are listed in Table II. This suggests that Wiberg's mechanism cannot be operating exclusively, but that another mechanism must also be involved.

Edwards and coworkers[10-13] have shown that per-

(6) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961); G. B. Payne, P. H. Deming, and P. H. Williams, *ibid.*, **26**, 659 (1961).

(7) This is consistent with the observation that acrylonitrile in carbonate buffer yields only "resinous products,"[8] whereas at pH 7.0–7.5 70% yields of the epoxyamide are isolated.[6]



(8) J. V. Murry and J. B. Cloke, *J. Amer. Chem. Soc.*, **56**, 2749 (1934); see also M. F. Shostakovskii and A. B. Bogdanova, *Chem. Abstr.*, **46**, 1961*f* (1952).

(9) J. O. Edwards and P. D. Fleischauer, *Inorg. Chem. Acta, Rev.*, **2**, 53 (1968).

(10) E. Koubek, G. Levy, and J. O. Edwards, *Inorg. Chem.*, **3**, 1331 (1964).

(11) E. Koubek, M. L. Haggett, C. J. Battaglia, K. M. Ibne-Rasa, H. Y. Pyun, and J. O. Edwards, *J. Amer. Chem. Soc.*, **85**, 2263 (1963).

(12) R. E. Ball, J. O. Edwards, M. L. Haggett, and P. Jones, *ibid.*, **89**, 2331 (1967).

(13) E. Koubek and J. E. Welsch, *J. Org. Chem.*, **33**, 445 (1968).

TABLE II
MASS SPECTRAL ANALYSIS OF OXYGEN GAS

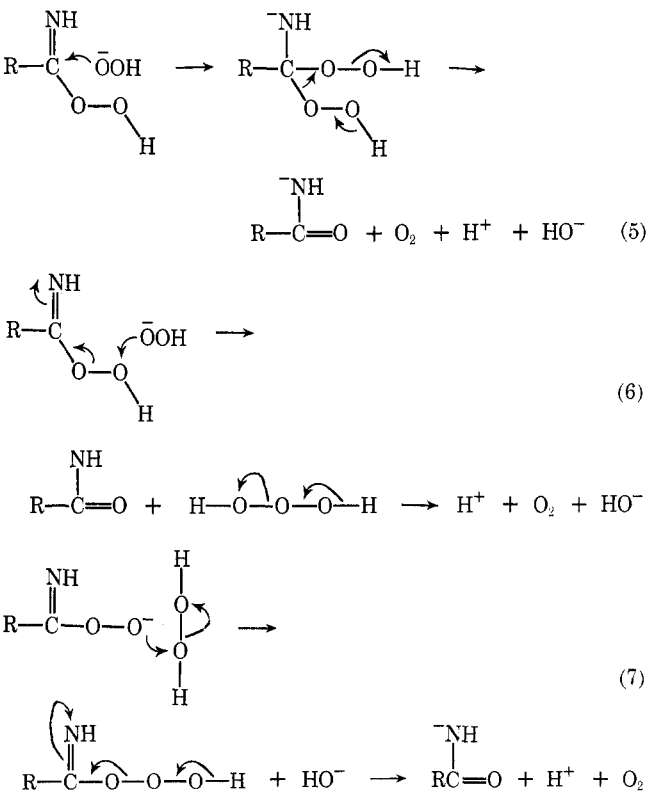
	Mole fractions		
	$^{32}O_2$	$^{34}O_2$	$^{36}O_2$
H_2O_2[a]	0.826	0.014	0.160
Reaction[b]	0.834	0.037	0.129

$$\text{Per cent unscrambled} = \frac{0.129}{0.160} \times 100 = 81\%$$

[a] Oxygen liberated by oxidation with Ce(IV) in 20% H_2SO_4 at 25°.[12] [b] In 0.1 M phosphate buffer containing 1×10^{-3} M EDTA at pH 7.4 in deionized water; T = 50–52°.

oxycarboxylic acids may decompose simultaneously *via* two distinctly different paths: (1) involving nucleophilic attack by the peroxy acid anion upon the carbonyl carbon of the peroxy acid (no scrambling) and (2) involving nucleophilic attack of the peroxy acid anion upon the outer oxygen of the peroxy acid (scrambling). For example, peroxyacetic acid decomposes 83% *via* path 1 and 17% *via* path 2.[11] When the carbonyl site is sterically hindered, as in the case of peroxypivalic acid, the results are reversed, 24% *via* path 1 and 76% *via* path 2.[13]

Because of the similarity in structure between I and peroxycarboxylic acids, we suggest that the fast step of the reaction can best be described by eq 5–7. Equation 5 predicts no scrambling, eq 7 predicts complete scrambling, and eq 6 predicts 50% scrambling. Edwards' work with peroxycarboxylic acids indicates that the transition states for paths 1 and 2 must be of similar energy; however, sp^2 carbon is the preferred site for attack.[14] In our case, since scrambling occurs, either eq 6 or eq 7 or both must be operative. We therefore conclude that eq 5 accounts for the major portion of the oxygen produced at pH 7.4. Under these conditions, if scrambling occurs only by eq 6, eq 5 will account for 62% of the reaction. If scrambling occurs only by eq 7, eq 5 will account for 81% of the reaction. Since the pK_a values of the peroxycarboximidic acid is probably in the vicinity of 8 (by analogy with peroxycarboxylic acids),[15] we expect that eq 7 will increase in importance at the expense of eq 5 and 6 at higher pH values. However, the complexity of the reaction at higher pH values, *vide ante*, would make the interpretation of double-labeling experiments in carbonate buffer or in sodium hydroxide solutions equivocal.



(5)

(6)

(7)

(14) The anion of hydrogen peroxide is an extremely powerful nucleophile toward the sp^2 carbon.[3]

Experimental Section

Kinetics were followed by monitoring the rate of loss of H_2O_2 by iodometric titration in the usual manner. A Warburg apparatus was used in those experiments for which the product of oxygen was followed.

Doubly labeled $H_2{}^{18,18}O_2$ was prepared by passing ^{18}O enriched H_2O (98 atom % ^{18}O, Miles-Yeda Ltd., Lot No. 18W97U) through an electric discharge tube.[16] The product $H_2{}^{18,18}O_2$ was rinsed from the cold traps with normal 30% H_2O_2 (Mallinkrodt, Lot WPBP) such that the resulting peroxide solution had an isotopic enrichment of 16 atom % of ^{18}O.

The *p*-cyanobenzoic acid (Aldrich Chemical Co., Lot No. 070671) was recrystallized twice from deionized water and treated with decolorizing charcoal. Deionized water was obtained by passing distilled water through a Barnsted mixed-bed ion exchange column. The mono- and dibasic potassium phosphate salts and the mono- and dibasic sodium carbonate salts used for buffer solutions were reagent grade. The disodium salt of EDTA was obtained from Eastman Organic Chemicals (Lot 681 A).

The reaction of the nitrile with hydrogen peroxide was carried out at 50–52°. Gas samples were collected at 2-hr intervals at a pressure of approximately 200 Torr at room temperature. Mass spectrometric analyses were performed on a Hitachi Perkin-Elmer RMU-6D instrument.

Registry No.—Hydrogen peroxide, 7722-84-1; *p*-cyanobenzoic acid, 619-65-8.

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(15) J. F. Goodman, P. Robson, and E. R. Wilson, *Trans. Faraday Soc.*, **86**, 1846 (1962).

(16) R. E. Ball, J. O. Edwards, and P. Jones, *J. Inorg. Nucl. Chem.*, **28**, 2458 (1966).

Nitrile Synthesis *via* the Acid–Nitrile Exchange Reaction

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Organic nitriles traditionally have been synthesized from the corresponding carboxylic acids by ultimate dehydration of the amide. Occasionally, the acid–nitrile exchange reaction has been used to accomplish direct conversion of carboxylic acids to nitriles by reaction with acetonitrile at high temperatures.[1,2] Apparently

(1) D. J. Loder, U. S. Patent 2,377,795 (1945).

(2) French Patent 1,525,498 (1968).