264. *The Elucidation of the Mechanism of the von Richter Reaction by Use of Oxygen-18 as Tracer.*

By David Samuel.

When substituted nitrobenzene derivatives are used in the von Richter reaction (formation of benzoic acids by the action of potassium cyanide in aqueous ethanol), the carboxyl group is found in the position *ortho* to that vacated by the nitro-group. *p*-Bromo- and *p*-chloro-nitrobenzene have now been used in ethanol–water (the latter enriched in oxygen-18). The *m*-bromo- and *m*-chloro-benzoic acid formed were isolated and analysed for their isotopic oxygen content. The results confirm the mechanism suggested by Bunnett and his co-workers in which a cyclic intermediate "imino-anhydride" (iminoisoxazoline) is formed.

von Richter[1] found that *m*-bromobenzoic acid is formed when *p*-bromonitrobenzene is heated with potassium cyanide in aqueous alcohol. Bunnett and his co-workers[2,3] found this to be a general reaction for substituted aromatic nitro-compounds, though not always giving good yields. They investigated the effects of varying the substituents, the medium, and the conditions of the reaction. Under the optimum conditions (refluxing 48% aqueous ethanol) *p*-chloronitrobenzene formed *m*-chlorobenzoic acid in about 40% yield, and nitrite was a by-product.

For all substituted nitrobenzenes the carboxyl group entered the position *ortho* to that vacated by the nitro-group. Reactions of this type, in which the entering group takes a position other than that vacated by the leaving group, have been named "cine" substitutions.[4] Bunnett and his co-workers[3] found that after reaction of nitrobenzene in D_2O–$C_2H_5{\cdot}OD$, the benzoic acid produced, contained (after equilibration of the carboxyl hydrogen atoms with ordinary water) 0·72 deuterium atom per molecule. The recovered nitrobenzene was nearly free from deuterium. Thus hydrogen atoms from the solvent become attached to the aromatic carbon in the course of the reaction. This exchange of hydrogen was confirmed[3] by using an aromatic nitro-compound labelled with deuterium in the aromatic ring and unlabelled solvent.

Various mechanisms have been proposed for the von Richter reaction. von Richter himself[1] and Lobry de Bruyn and van Geuns[5] suggested the formation of an intermediate nitrobenzonitrile which loses the nitro-group as nitrite by an unspecified mechanism. The substituted benzonitrile is then hydrolysed to a benzoic acid. In no case has such an intermediate been isolated, though when aromatic nitriles are added to the reacting mixture[6] they are rapidly hydrolysed to a mixture of acid and amide.

On the basis of all the observed facts Bunnett and Rauhut[6] proposed the annexed mechanism for the von Richter reaction. They suggested that step (1) is slow, its rate, and hence the over-all yield of acid, being affected by the other substituents. Step (3) involves the formation of an "imino-anhydride" (iminoisoxazoline) (III) which is hydrolysed in step (4) to a cyclic mixed anhydride (IV). Step (6) accounts for the exchange of deuterium between the aromatic ring and the solvent. Intermediates (III) and (IV) are of a novel type. The mechanism of the von Richter reaction has now been investigated by using as solvent a mixture of ethanol and water enriched in oxygen-18. Under the basic conditions of the reaction, there is no exchange between alcohol and water.[7] If Bunnett's

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[1] von Richter, *Ber.*, 1871, **4**, 21, 459, 553; 1874, **7**, 1145; 1875, **8**, 1418.

[2] Bunnett, Cormack, and McKay, *J. Org. Chem.*, 1950, **15**, 481; Bunnett and Rauhut, *ibid.*, 1956, **21**, 934; Bunnett, *ibid.*, p. 939.

[3] Bunnett, Rauhut, Knutson, and Bussel, *J. Amer. Chem. Soc.*, 1954, **70**, 5755.

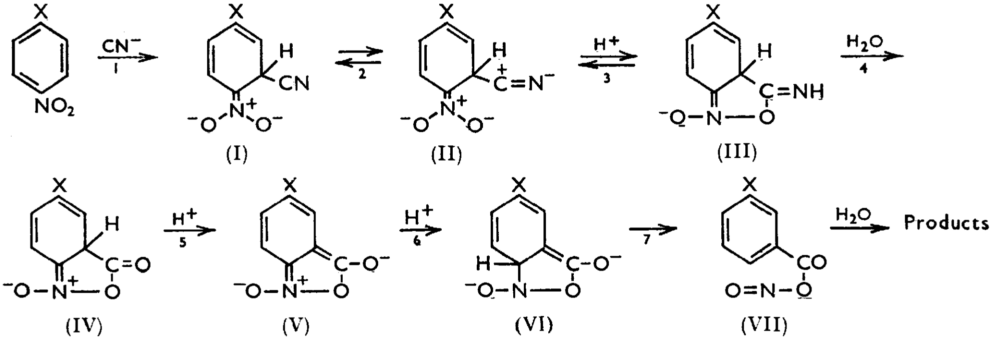
[4] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 382; Bunnett, *Quart. Rev.*, 1958, **12**, 1.

[5] Lobry de Bruyn and Van Geuns, *Rec. Trav. chim.*, 1904, **23**, 26, 47.

[6] Bunnett and Rauhut, *J. Org. Chem.*, 1956, **21**, 944.

[7] Anbar, Dostrovsky, Samuel, and Yoffe, *J.*, 1954, 3603.

mechanism is correct, the cyclic anhydride (IV) will contain one oxygen atom in the carbonyl group from the water in the solvent, formed by hydrolysis of the imino-anhydride (III), the " bridging " oxygen atom being one of those of the original nitro-group. In step (7) the carbon–nitrogen bond is broken and a carboxylic–nitrous anhydride (VII) is formed. It has been shown [7] that esters of nitrous acid are hydrolysed by nucleophilic attack on nitrogen (*i.e.*, an S_NX reaction) with N–O cleavage. It seems reasonable to suppose that mixed anhydrides will also be hydrolysed with N–O cleavage and the final product, a substituted benzoic acid, will contain one oxygen atom from the solvent enriched in ^{18}O and one from the nitro-group with a normal ^{18}O abundance.



p-Chloronitrobenzene was caused to react in refluxing 48% and in 95% ethanol, the latter in order to eliminate any confusion due to a 1 : 1 ratio of ethanol to ester in the solvent. The reaction was also run with *p*-bromonitrobenzene in a sealed tube in 48% aqueous ethanol at 150°. The products and unchanged starting material were isolated under conditions where no exchange of oxygen could occur, and were analysed for oxygen-18 content. The results are in the Table, together with those calculated on the assumption that one oxygen atom comes from the water in the solvent and one from the nitro-group. They show that there is virtually no exchange of oxygen between water and aromatic nitro-compounds under the conditions of the experiments.

Expt.	Nitro-compound	Solvent	Conditions	At. % ^{18}O in H_2O of solvent	At. % ^{18}O in recovered nitro-cpd.	At. % ^{18}O in acid	
						Found	Calc.
A	p-$C_6H_4Br{\cdot}NO_2$	48% EtOH	150°, 1 hr.	1·53	0·20	0·84	0·86
B	p-$C_6H_4Cl{\cdot}NO_2$	,,	B. p., 18 hr.	1·53	0·20	0·83	0·86
C	,,	95% EtOH	B. p., 48 hr.	1·32	0·23	0·70	0·76

If the mechanisms proposed by von Richter [1] and by Lobry de Bruyn and van Geuns [5] were correct the benzoic acids formed should contain the same atom % ^{18}O as the water in the solvent. The isotopic results therefore eliminate any mechanism involving the hydrolysis of an intermediate benzonitrile. The agreement between the observed and the calculated results confirms the mechanism proposed by Bunnett and Rauhut.[6]

EXPERIMENTAL

Materials.—*p*-Chloronitrobenzene and *p*-bromonitrobenzene were commercial products, purified by recrystallization from ethanol.

^{18}O-Enriched water (1·58 at. % ^{18}O) was obtained from the distillation plant of the Weizmann Institute of Science. Aqueous-ethanol solvents were made up by volume from this water and absolute ethanol.

Isotopic Analyses.—*p*-Chloronitrobenzene, *p*-bromonitrobenzene, and *m*-chlorobenzoic acid were analysed by an adaptation of the method of Anbar and Guttmann.[8] The compound (~20 mg.) is introduced into a borosilicate tube (2 ml.) with a break off-top and a seal-off constriction containing a 1 : 1 mixture (~300 mg.) of mercuric chloride and mercuric cyanide. The tube and both the salts should be vacuum-dried and as free from absorbed moisture as possible. The tube is evacuated and sealed off, then heated at 400° for 2 hr. After cooling, the tube is opened on a vacuum-line and the gases formed are condensed by cooling with liquid nitrogen into a second tube of the same design containing saturated zinc amalgam (~2 g.). The non-condensable gases formed are pumped off. The second tube is sealed off under a vacuum and heated at 200° for 2 hr.

This treatment removes cyanogen, hydrogen chloride, and other impurities which react with the zinc. On cooling, the material is ready for analysis by mass-spectrometry.

The atom % ^{18}O was calculated from the peaks of masses 44 and 46 by means of the equation (used for fairly low concentrations of ^{18}O):

$$\text{Atom \% }^{18}\text{O} = \frac{\text{Peak 46/Peak 44}}{2 + \text{Peak 46/Peak 44}}$$

Water and the water in the aqueous-alcoholic mixtures were analysed by equilibration with carbon dioxide in a borosilicate tube at 70° for 12 hr.

von Richter Reactions.—Conditions and quantities were essentially those described by Bunnett and his co-workers[3] except that ^{18}O-enriched water was used in the solvent and working up was modified to eliminate the possibility of exchange of oxygen during purification. Results are in the preceding Table.

(*A*) *p*-Bromonitrobenzene (4 g.), potassium cyanide (2·6 g.), and 48% aqueous ethanol (25 ml., containing ^{18}O-enriched water) were heated in a sealed tube for 1 hr. at 150°. On cooling, the dark red contents were made basic with potassium hydroxide and steam-distilled to remove unchanged starting material and ethanol. The solid *p*-bromonitrobenzene (1·1 g.) was filtered off, recrystallised (m. p. 128—128·5°) from ethanol, and analysed for ^{18}O. The residual solution from the steam-distillation was cooled, made acid with aqueous nitric acid (1 : 1), and extracted rapidly six times with ether. The combined ether extracts were dried (Na_2SO_4) and the solvent was removed. The dark solid was then sublimed at ~110°/0·01 mm. The sublimed material (0·6 g.) was recrystallised from ether–hexane; it had m. p. 158—158·5° and was analysed for ^{18}O.

(*B*) *p*-Chloronitrobenzene (3·15 g.) and potassium cyanide (10·3 g.) were refluxed in 48% ethanol (75 ml., containing ^{18}O-enriched water) for 18 hr. The dark red solution was worked up as described in (*A*). The recovered *p*-chloronitrobenzene (0·6 g.) was recrystallised (m. p. 84—84·5°) from ethanol and analysed for ^{18}O. The *m*-chlorobenzoic acid was separated from tar, etc., by sublimation followed by recrystallisation (m. p. 156—157°) from ether–hexane and analysed for ^{18}O.

(*C*) *p*-Chloronitrobenzene (3·15 g.) and potassium cyanide (20 g.) were refluxed in 95% ethanol (75 ml., containing ^{18}O-enriched water) for 48 hr. A considerable part of the potassium cyanide remained unchanged. The dark red solution was decanted and worked up as described above. The recovered *p*-chloronitrobenzene (0·4 g.) was recrystallised (m. p. 156—157°), from ethanol, and *m*-chloronitrobenzene was sublimed and recrystallised (m. p. 156°) from ether–hexane before analysis for ^{18}O.

THE ISOTOPE DEPARTMENT, THE WEIZMANN INSTITUTE OF SCIENCE,
REHOVOTH, ISRAEL.

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[8] Anbar and Guttmann, *J. Internat. Appl. Radn. Isotopes*, 1959, **4**, 234.