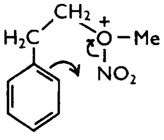
759. *The* ortho : para-*Ratio in Aromatic Substitution. Part V.*[1] *Nitration by Mixed Acid and Acetyl Nitrate.*

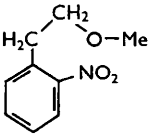
By J. R. Knowles and R. O. C. Norman.

The isomer distributions obtained in the nitration of a series of benzylic compounds with mixed acid are reported and are compared with the known ratios given by these compounds when acetyl nitrate is the reagent. There is evidence that some nitration of the conjugate acid occurs in the nitration by mixed acid of compounds containing basic sites in the side-chain. With acetyl nitrate, *ortho*-reactivity is enhanced, by a mechanism proposed previously, to a degree depending on the nucleophilicity of the heteroatom in the side-chain and on stereochemical factors.

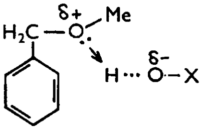
A mechanism has recently been proposed [2] to account for the different isomer distribution observed in the nitration of methyl phenethyl ether by acetyl nitrate from that obtained with mixed acid. It was postulated that the high *ortho* : *para*-ratio obtained with acetyl nitrate is due to an additional mode of nitration, concomitantly with " normal " nuclear nitration by the nitronium ion. The first step of this is an S_N2 displacement of nitrate ion from covalent dinitrogen pentoxide (the presence of which is well established in acyl nitrate solutions [3]) by the oxygen atom of the ether. The charged intermediate formed (I) then rearranges through a six-membered cyclic transition state to yield the *o*-nitro-isomer (II).



(I)



(II)



(III)

---

[1] Part IV, Billing and Norman, preceding paper.

[2] Norman and Radda, *Proc. Chem. Soc.*, 1960, 423; *J.*, 1961, 3030.

[3] Chèdin and Fénéant, *Compt. rend.*, 1949, **229**, 115; Malkova, *J. Gen. Chem.* (*U.S.S.R.*), 1954, **24**, 1151; Vandoni and Viala, *Mém. Services chim. État*, 1945, **32**, 80.

Since the crucial step in this mechanism is the S_N2 displacement on dinitrogen pentoxide by a nucleophilic atom in the side-chain of the aromatic compound, it was of interest to investigate the behaviour in nitration of other aromatic compounds with and without nucleophilic atoms in the side-chain. Isomer ratios for the nitration by acetyl nitrate of toluene, ethyl phenylacetate, benzyl methyl ether, benzyl chloride, benzyl cyanide, and phenylnitromethane have already been reported,[4] and these ratios are compared in Table 1 with those obtained by nitration of these compounds with 1 : 1 mixed acid. Values for the nitration of methyl phenethyl ether,[2] and methyl 3-phenylpropyl ether,[5] are included in this Table.

TABLE 1. *Isomer ratios obtained by nitration with acetyl nitrate and mixed acid.*

	$AcO{\cdot}NO_2$			1 : 1 HNO_3–H_2SO_4		
	o- (%)	*m*- (%)	*p*- (%)	*o*- (%)	*m*- (%)	*p*- (%)
Toluene	56·1	2·5	41·4	56·0	2·4	41·6
Ethyl phenylacetate	54·3	13·1	32·6	41·7	24·6	33·7
Benzyl methyl ether	51·3	6·8	41·9	28·6	18·1	53·3
Benzyl chloride	33·6	13·9	52·5	34·4	14·1	51·5
Benzyl cyanide	24·4	20·1	55·5	22·0	20·7	57·3
Phenylnitromethane	22·5	54·7	22·8	22·2	53·1	24·7
Methyl phenethyl ether	62·3	3·7	34·0	31·6	9·4	59·0
Methyl 3-phenylpropyl ether	44·2	3·8	52·0	37·3	5·9	56·8

Three factors should govern the isomer ratios cited.

First, with both of the nitrating agents used, direct nuclear nitration occurs *via* the nitronium ion, which is known to be present in both solutions.[6] Nitration by *this ion* should give rise to the same orientations under both nitrating conditions.[7]

Secondly, in mixed acid solutions there is a high concentration of protons, and the orientation will be affected if a basic site in the side-chain of the aromatic compound becomes protonated. [We shall refer to " protonation " and " positive species," but proton transfer may be by no means complete. However, the arguments presented are still valid for a high degree of polarisation of the unshared electrons of the basic site by the acid medium (III); cf. ref. 8.] Although the positive ion produced will be much less reactive towards electrophilic reagents than its conjugate base, some of the total nitration observed may be that of the 'onium ion. The change in orientation will be governed both by the degree of insulation of the positive charge of the protonated form from the aromatic ring (*i.e.*, the reactivity of the positive species) and by the total degree of protonation of the parent compound (*i.e.*, the concentration of the positive species).

Thirdly, in acetyl nitrate solutions, the presence of dinitrogen pentoxide should enable specific *ortho*-nitration to occur if (*a*) there is a suitable nucleophilic site in the side-chain, and (*b*) the charged intermediate produced by the attack of this nucleophilic site on dinitrogen pentoxide is stereochemically suited to rearrange to the *o*-nitro-isomer.[2]

On the basis of these expectations, the observed orientations in Table 1 can be accounted for.

Protonation.—Protonation in the side-chain will reduce the reactivity of the *ortho*- and *para*-positions more than of the *meta*-position, and thereby increase the $\frac{1}{2}m : p$-ratio relative to that for the conjugate base. Values of $\frac{1}{2}m : p$ (mixed acid)/$\frac{1}{2}m : p$ (acetyl nitrate) greater than one are therefore diagnostic of some nitration of the conjugate acid. This ratio will be determined by three factors: the number of methylene groups between the positive charge and the ring (cf. the proportion of *meta*-derivative formed in the

---

[4] Knowles and Norman, *J.*, 1961, 2938.

[5] G. K. Radda, unpublished results.

[6] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, p. 270; Paul, *J. Amer. Chem. Soc.*, 1958, **80**, 5329.

[7] *E.g.*, Ingold, Lapworth, Rothstein, and Ward, *J.*, 1931, 1959.

[8] Gordy and Stanford, *J. Chem. Phys.*, 1941, **9**, 204.

nitration of $Ph\cdot NMe_3^+$, $Ph\cdot CH_2\cdot NMe_3^+$, and $Ph\cdot[CH_2]_2\cdot NMe_3^+$ [9]); the proton-affinity of the heteroatom (which determines the concentration of the conjugate acid); and the reactivity of the conjugate base (the more reactive this is, the smaller will be the contribution to the total nitration of reaction of the conjugate acid; thus aniline is nitrated predominantly through the much more reactive unprotonated form in strongly acid solution [10]).

Evidence that these three factors operate in the systems studied here is seen by inspection of the $\frac{1}{2}m:p$ (mixed acid)/$\frac{1}{2}m:p$ (acetyl nitrate)-ratios (henceforward, " R ") set out in Table 2.

TABLE 2. m : p- *and* o : p-*Ratios.*

	PhMe	Ph·CH₂– Cl	Ph·CH₂– NO₂	Ph·CH₂– CN	Ph·CH₂– CO₂Et	Ph·CH₂– OMe	Ph·[CH₂]₂– OMe	Ph·[CH₂]₃– OMe
$\frac{1}{2}m:p$ (mixed acid) ...	0·029	0·14	1·07	0·18	0·36	0·17	0·080	0·052
$\frac{1}{2}m:p$ (acetyl nitrate)	0·030	0·13	1·20	0·18	0·20	0·08	0·054	0·036
$\dfrac{\frac{1}{2}m:p \text{ (mixed acid)}}{\frac{1}{2}m:p \text{ (acetyl nitrate)}}$	1·0	1·1	0·9	1·0	1·8	2·1	1·5	1·4
$\frac{1}{2}o:p$ (acetyl nitrate)	0·68	0·32	0·49	0·22	0·83	0·61	0·92	0·42
$\frac{1}{2}o:p$ (mixed acid) ...	0·67	0·33	0·45	0·19	0·62	0·27	0·27	0·33
$\dfrac{\frac{1}{2}o:p \text{ (acetyl nitrate)}}{\frac{1}{2}o:p \text{ (mixed acid)}}$	1·0	1·0	1·1	1·1	1·3	2·3	3·4	1·3

(i) Toluene, which has no heteroatom, shows no change in orientation (" R " = 1).

(ii) In the series $Ph\cdot CH_2\cdot OMe$, $Ph\cdot[CH_2]_2\cdot OMe$, $Ph\cdot[CH_2]_3\cdot OMe$, as the number of methylene groups between the heteroatom and the nucleus increases, the change in orientation becomes proportionately less (" R " = 2·1, 1·5, 1·4, respectively).

(iii) The proton-affinities of basic groupings studied by Gordy and Stanford [8] (by measurement of the frequency shift of the O–D band of $CH_3\cdot OD$ in the basic compound from the " unimolecular " band of $CH_3\cdot OD$ in benzene solution) lie in the order: chloro- < nitro- < cyano- < ester < ether (*e.g.*, the shifts for acetonitrile, ethyl acetate, and diethyl ether are 63, 84, and 130 cm.$^{-1}$, respectively). Within experimental error this order is followed here. Benzyl chloride, benzyl cyanide, and phenylnitromethane, which are the most weakly basic, show no evidence of nitration through the protonated species (" R " = 1); and for ethyl phenylacetate and benzyl methyl ether, which are of comparable nuclear reactivity,[4] " R "-values are in the order of proton-affinities.

Specific ortho-*Interaction.*—That protonation in mixed acid cannot explain the change in *ortho* : *para*-ratios with change of nitrating conditions may be shown by the following argument. For the nitration of the conjugate acid of benzyl methyl ether, suppose that (by analogy with $Ph\cdot CH_2\cdot NMe_3^+$ [9]) the proportion of *meta*-derivative is 80%. Then from the observed change in the orientation from acetyl nitrate to mixed acid, the contribution to the total nitration of reaction of the conjugate acid is about 12%. If we assume the extreme case, that nitration of the conjugate acid gives *no ortho*-derivative, the proportion of *o*-nitro-compound, obtained by nitrating with acetyl nitrate, arising solely from reaction of the unprotonated form, would be 33%. The observed proportion is considerably higher than this (51·3%) and confirms the operation of some specific *ortho*-interaction with acetyl nitrate. (Further evidence for this, from the changes in *meta* : *para*- and *ortho* : *para*-ratios with increasing acidity of the nitrating medium, is cited in ref. 2.)

Support for this conclusion comes from the $\frac{1}{2}o:p$(acetyl nitrate)/$\frac{1}{2}o:p$(mixed acid)-ratios (henceforward, " S ") for the ethers. Whereas " R "-values fall off in the order: $Ph\cdot CH_2\cdot OMe$, $Ph\cdot[CH_2]_2\cdot OMe$, $Ph\cdot[CH_2]_3\cdot OMe$, " S "-values show a maximum (" S " = 2·3, 3·4, 1·3, respectively) for $Ph\cdot[CH_2]_2\cdot OMe$. This is consistent with the operation of

---

[9] Vorlander and Siebert, *Ber.*, 1919, **52**, 294; Goss, Ingold, and Wilson, *J.*, 1926, 2440; Goss, Hanhart, and Ingold, *J.*, 1927, 250.

[10] Hughes and Jones, *J.*, 1950, 2678.

the cyclic mechanism previously proposed for enhancement of reactivity at the *ortho*-position of methyl phenethyl ether,[2] together with the stereochemical requirement that the ease of rearrangement [*e.g.*, of (I) to (II)] depends on the ring-size of the cyclic transition state. The order of " S "-values suggests that this is $6 > 5 > 7$.

Apart from this stereochemical requirement, increase in *ortho*-reactivity by this mechanism depends on the presence of a nucleophilic atom in the side-chain. It is well known [11] that the nucleophilicity of a given atom (*e.g.*, oxygen) in different electronic environments parallels its basicity. It is therefore understandable that this *ortho*-effect (measured by " S "-values) for those compounds which satisfy the stereochemical requirement for rearrangement, falls off in the same order as the proton-affinities of the groupings (that is, $Ph{\cdot}[CH_2]_2{\cdot}OMe > Ph{\cdot}CH_2{\cdot}CO_2Et > Ph{\cdot}CH_2{\cdot}NO_2$).

Experimental.—Nitration was carried out at 25° with a 1 : 1 (v/v) mixture of nitric (" AnalaR," *d* 1·5) and sulphuric acid (" AnalaR," *d* 1·84). Reference materials, extraction procedures, and methods of analysis have been previously described.[4] The isomer distributions in Table 1 are mean values of at least three analyses in each case; the mean deviation is ±0·8% for all compounds except ethyl phenylacetate and benzyl methyl ether, for which it is ±1·5%.

One of us (J. R. K.) thanks Christ Church for a Research Lectureship.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, April 5th,* 1961.]

[11] Hine, " Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1956, p. 138.