440. *Aromatic Azo-compounds. Part I. Oxidation of* cis- *and* trans-*Azobenzene.*

By G. M. Badger, R. G. Buttery, and G. E. Lewis.

The oxidation of *cis*-azobenzene with perbenzoic acid has given *cis*-azoxybenzene; *cis*-azoxy-compounds have also been obtained by oxidation of *cis-m*-azotoluene and *cis-p*-azotoluene. Reduction of *cis*-azoxybenzene with lithium aluminium hydride, however, gave *trans*-azobenzene. *trans*-Azobenzene gave *trans*-azoxybenzene on oxidation in the dark, but some *cis*-azoxybenzene was obtained on oxidation in sunlight.

A method has been developed for studying the rates of reaction of azo-compounds with perbenzoic acid, and *cis*-azobenzene has been shown to react very much more rapidly than the *trans*-compound. The results indicate that the electron density at the azo-linkage in *cis*-azobenzene is much greater than that in the *trans*-isomer.

The aromatic azo-compounds are of considerable importance, particularly in connection with the study of the relationship between chemical constitution and colour. Many useful dyes belong to this class, and some azo-compounds have proved to be of medicinal value. In addition, certain aminoazo-compounds have been shown to produce liver tumours when administered for long periods to experimental animals. *o*-Aminoazotoluene and 4-dimethylaminoazobenzene behave in this way, and although numerous related compounds are known to be liver carcinogens, a relatively specific structure seems to be required (Badger and Lewis, *Brit. J. Cancer*, 1952, in the press). Pullman (*Compt. rend.*, 1946, **222**, 1501; 1947, **224**, 1773; Pullman and Pullman, *Rev. Sci.*, 1946, **84**, 145) has suggested that carcinogenic activity is associated with an optimum density of electrons at the azo-linkage (called the *K'* region) and that the magnitude of the charge is governed by the substituents present. It seemed of interest to examine this hypothesis experimentally, and the work reported in the present series of papers was undertaken to this end.

Other things being equal, the greater the electron density at the nitrogen atoms, the greater the reactivity towards electrophilic reagents. It therefore seemed that a suitable method would be to study the rate of addition of an electrophilic reagent to the *K'* region in a series of carcinogenic and related non-carcinogenic azo-compounds. The per-acids are known to be electrophilic reagents (Swern, *J. Amer. Chem. Soc.*, 1947, **69**, 1692; *Chem. Reviews*, 1949, **45**, 1; Derbyshire and Waters, *Nature*, 1950, **165**, 401), and a method for the determination of the rate of reaction of azo-compounds with perbenzoic acid has accordingly been developed (for a preliminary account of some of this work, see Badger and Lewis, *ibid*, 1951, **167**, 403).

Boëseken and Stuurman (*Rec. Trav. chim.*, 1937, **56**, 1034) studied the rate of oxidation of various ethylenic compounds with peracetic acid, and the experimental procedure now used was based on their method. The reactions were carried out in benzene solution, at constant temperature, perbenzoic acid being used. Aliquot portions of reaction mixture were removed at suitable intervals, and the residual perbenzoic acid estimated by titrating the iodine liberated from acidified potassium iodide solution with standard sodium thiosulphate solution.

Much higher reaction rates were obtained when using samples of perbenzoic acid which had undergone an appreciable degree of spontaneous decomposition. This was interpreted as a catalytic effect caused by the presence of benzoic acid, and it was confirmed by studying the rate of oxidation of azobenzene with a mixture containing equimolecular proportions of benzoic and perbenzoic acids, a significant increase in the rate of reaction being observed. A similar catalytic effect of benzoic acid has already been noted by Friess (*J. Amer. Chem. Soc.*, 1949, **71**, 2571). For this reason, only freshly prepared solutions of perbenzoic acid were used for all rate determinations.

The rate of reaction was also increased when the reaction mixtures were exposed to the ordinary light. Reproducible results could only be obtained when the reactions were carried out in flasks which had been well covered with a black enamel.

trans-Azobenzene is known to be converted into an equilibrium mixture of *cis*- and *trans*-azobenzene by light, and it is likely that the catalytic effect of light in the perbenzoic acid oxidation might be associated with this fact, since *cis*-azobenzene reacts very much more rapidly than the *trans*-azo-compound (see below).

The oxidation of *trans*-azobenzene was carried out at four different temperatures, and in each case at least three runs were made with wide variations in the $(a - b)$ factor. The reactions were followed to at least 50% completion, and the results (Tables 1, 2, and 3) indicate that the reaction is of the second order. *cis*-Azobenzene has also been studied at four temperatures, in the dark, and the rate constants are included in Table 2. *cis*-Azobenzene is slowly transformed into the stable *trans*-form ; it has been shown, however, that the half-life of the *cis*$\longrightarrow$*trans*-transformation in the dark is 119 hr. at 25° (Hartley, *J.*, 1938, 633), and as the oxidation proceeds very rapidly, this transformation cannot have an appreciable effect.

TABLE 1. *Reaction between* trans-*azobenzene and perbenzoic acid in benzene solution at* 25°.

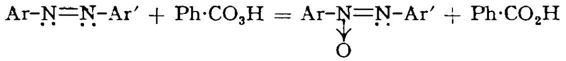
$(a - b)$, mole/l.	0·00158	0·00335	0·01812
10^3k_2, mole^{-1} min.$^{-1}$ l.	13·8 ± 0·3	14·1 ± 0·2	13·9 ± 0·3
		Mean :	13·9 ± 0·3

TABLE 2. *Rate constants and activation energies for reaction between* cis- *and* trans-*azobenzene and perbenzoic acid.**

	10^3k_2 (mole^{-1} min.$^{-1}$ l.)				ΔH			
Azobenzene	15°	20°	25°	30°	(kcal.)	X	Y	Z
trans-	5·80±0·07	9·02±0·15	13·9±0·03	20·9±0·03	14·8±0·3	0	0	0
cis-	374±6	527±9	749±11	1085±25	12·3±0·5	−2·5	−0·1	−2·4

* ΔH_0, ΔS_0, and ΔF_0 are the heat of activation, the entropy of activation, and the free energy of activation, respectively, for *trans*-azobenzene. $X = \Delta H^{\ddagger} - \Delta H_0{}^{\ddagger}$; $Y = T(\Delta S^{\ddagger} - \Delta S_0{}^{\ddagger})$; $Z = \Delta F^{\ddagger} - \Delta F_0{}^{\ddagger}$; all in kcal. The quantities $T(\Delta S^{\ddagger} - \Delta S_0{}^{\ddagger})$ and $\Delta F^{\ddagger} - \Delta F_0{}^{\ddagger}$ are calculated from the data at 25°.

trans-Azoxybenzene was isolated in almost quantitative yield from the products of oxidation of *trans*-azobenzene with perbenzoic acid in the dark, and the reaction may therefore be represented by the equation :



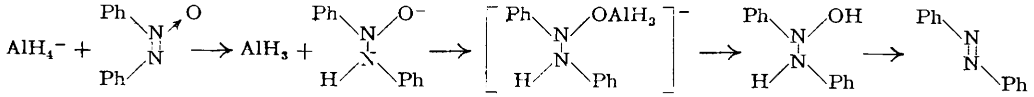
$$\text{Ar-}\ddot{\text{N}}\text{=}\ddot{\text{N}}\text{-Ar}' + \text{Ph·CO}_3\text{H} = \text{Ar-}\underset{\substack{\downarrow\\ \text{O}}}{\text{N}}\text{=}\ddot{\text{N}}\text{-Ar}' + \text{Ph·CO}_2\text{H}$$

cis-Azoxybenzene is rapidly converted into the more stable *trans*-form, especially in sunlight and at high temperatures : it may be noted that Cook and Jones (*J.*, 1941, 184) isolated only *trans*-azoxybenzene from the oxidation of *cis*-azobenzene with peracetic acid. *cis*-Azoxybenzene has now been isolated, however, following oxidation of *cis*-azobenzene with perbenzoic acid. The oxidation was carried out at room temperature in the dark, concentrations being such as to enable the reaction to proceed almost to completion within 3 hr. Even under these conditions, some *trans*-azoxybenzene was also isolated. *cis*-Azoxybenzene has also been isolated from the products of oxidation of excess of *trans*-azobenzene with a concentrated solution of perbenzoic acid, in sunlight ; and this confirms the interpretation, given above, for the catalytic effect of light in this reaction.

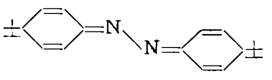
The method has also been extended to two other compounds, and in qualitative experiments, *cis*-azoxy-compounds have been produced by oxidation of *cis-m-* and of *cis-p*-azotoluene with perbenzoic acid.

Although there was no doubt as to the structures of these compounds (Hartley and Le Fèvre, *J.*, 1939, 531 ; Calderbank and Le Fèvre, *J.*, 1948, 1949), this seems to be the first time that the *cis*-azo-compounds have been directly related to the *cis*-azoxy-compounds.

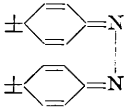
trans-Azoxybenzene is known to give *trans*-azobenzene on reduction (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738), and the inter-relationship would be completed if *cis*-azoxybenzene could be reduced to *cis*-azobenzene. It has been found, however, that reduction of *cis*-azoxybenzene with lithium aluminium hydride yields only *trans*-azobenzene. This result is of some importance, as it suggests that the reduction must proceed *via* an intermediate having a single bond between the nitrogen atoms. Such an intermediate would have free rotation about this bond, and the more stable *trans*-form of the azo-compound would naturally be formed. By analogy with the postulated mechanism for the reduction of epoxides with lithium aluminium hydride (Brown, *Org. Reactions*, 1951, **6**, 469), it is suggested that the aluminohydride ion adds to the azoxy-compound, and that subsequent decomposition gives the *trans*-azo-compound in accordance with the following scheme :



Discussion.—The structures and molecular dimensions of both the *cis*- and the *trans*-form of azobenzene have been determined by quantitative *X*-ray investigation (de Lange, Robertson, and Woodward, *Proc. Roy. Soc.*, 1939, *A*, **171**, 398; Robertson, *J.*, 1939, 232; Hampson and Robertson, *J.*, 1941, 409). The *trans*-azobenzene molecule is very nearly coplanar. The N=N bond is 1·23 Å long, and the C–N bonds 1·41 Å. As the normal C–N single-bond distance is 1·47 Å, and the normal C=N double-bond distance 1·28 Å, structures such as (I) must make a considerable contribution to the normal state of the molecule. The N=N bond must therefore have some single-bond character and the C–N bonds some double-bond character. According to Buu-Hoï *et al.* (*Bull. Soc. chim.*, 1951, **18**, 132c), the N=N bond has a bond order of 1·746, and the C–N bonds an order of 1·470. In addition, the two nitrogen " lone pairs " must also be shared to some extent with the ring systems, and the net result is that the electron density around the N=N linkage must be considerably below the value expected in the absence of such conjugation.



(I)



(II)

The *cis*-azobenzene molecule, on the other hand, is not coplanar. Owing to steric effects, the two benzene rings are rotated about 50° from the planar positions. The N=N bond is 1·23 Å long and the C–N bonds were found to be 1·46 Å, almost identical with the length of normal C–N single bonds. The departure from coplanarity has therefore led to a suppression of conjugation, and structures such as (II) cannot contribute significantly to the resonance hybrid. The net result must be that the electron density around the N=N linkage in *cis*-azobenzene is much greater than that in the *trans*-compound.

On oxidation with perbenzoic acid, both azobenzenes are converted into the azoxy-compounds. The N–O bond is known to be of the co-ordinate covalent type, and an essential feature of the reaction must therefore be the localisation of two electrons at one of the nitrogen atoms. It is reasonable to suppose that the energy required to bring about this localisation will be a major part of the activation energy for the reaction. Furthermore, other things being equal, the greater the initial electron density on the nitrogen atom, the less the energy required to localised the two electrons.

The results summarised in Table 2 indicate that *cis*-azobenzene is oxidised very much more rapidly than the *trans*-compound. The entropies of activation ($\Delta S^{\ddagger}$) are essentially the same, and the heat of activation ($\Delta H^{\ddagger}$) and the free energy of activation ($\Delta F^{\ddagger}$) are significantly smaller in the case of *cis*-azobenzene. It may be concluded, therefore, that the oxidation results confirm the greater electron density and electron availability at the N=N linkage in the *cis*-compound.

EXPERIMENTAL

Materials.—" AnalaR " benzene was used in all kinetic experiments. Perbenzoic acid was prepared by Brooks and Brooks's method (*J. Amer. Chem. Soc.*, 1933, **55**, 4309) except that " AnalaR " benzene was used instead of chloroform to extract the per-acid. Fresh perbenzoic acid was prepared for each series of determinations, and when not in use the solution was kept in the refrigerator. After several recrystallisations from alcohol, commercial *trans*-azobenzene had m. p. 68°. It was further purified chromatographically by adsorption on alumina from light petroleum solution and elution with light petroleum–benzene. No bands due to impurities were obtained. After a further recrystallisation from alcohol, *trans*-azobenzene, m. p. 68°, was obtained, and this was used in all the kinetic experiments. *cis*-Azobenzene was prepared according to Hartley (*J.*, 1938, 633); after recrystallisation from light petroleum (b. p. $<45°$) it had m. p. 71°.

Reaction.—The accurately weighed azo-compound (0·5, 0·75, or $1·0 \times 10^{-3}$ mole) was dissolved in " AnalaR " benzene in a standard flask (25·0 or 50·0 ml.) well covered with black enamel, and the flask placed in the thermostat. The stock solution of freshly prepared 0·5—0·7N-perbenzoic acid was also placed in the thermostat, and when equilibrium had been attained, 5·00 ml. were added to the solution of azo-compound, with gentle mixing. The time of half-addition was taken as zero time. The solution was quickly made up to the mark with " AnalaR " benzene at the temperature of the reaction, and the mixture vigorously shaken. An aliquot portion was then quickly removed, and the perbenzoic acid concentration estimated by titration of the iodine liberated from acidified potassium iodide against standard sodium thiosulphate. Further aliquots were removed at suitable time intervals, the time for each reading being taken at the instant of the addition and mixing with the potassium iodide solution. As a rule, the first reading was taken 3—4 min. after zero time, and the initial concentration of per-acid was therefore determined by extrapolation of the plot of the remaining per-acid concentration against the time. The reaction was followed to at least 50% of completion, and second-order rate constants were calculated.

Table 3 records the results obtained in a typical run with *trans*-azobenzene. In this experiment, $1·0 \times 10^{-3}$ mole of azobenzene was used in a reaction mixture totalling 25·0 ml. 2·0-ml. samples were withdrawn at intervals and titrated with N/40-sodium thiosulphate; k_2 is given in mole^{-1} min.$^{-1}$ l.

TABLE 3. *Typical run with* trans-*azobenzene, at 25°.*

Time, min. ...	0	3	31	108	227	362	495	1358	1676	2090	3030
Titre, ml. ...	(9·30) *	9·29	9·14	8·77	8·28	7·81	7·40	5·73	5·30	4·83	4·29
10^3k_2	—	—	13·94	14·24	13·94	13·80	13·79	13·49	13·78	14·35	13·73

Mean 13·90 ±

* By extrapolation.

trans-*Azoxybenzene.*—When the reaction with *trans*-azobenzene was virtually complete, the reaction mixture was washed with dilute sodium carbonate solution, and then with water, and dried. After evaporation of the solvent, the product was purified by chromatography on alumina from light petroleum solution. It was identified as *trans*-azoxybenzene, m. p. 36°, by direct comparison with an authentic specimen.

cis-*Azoxybenzene.*—(i) *cis*-Azobenzene (1·5 g.) was added to a 0·78N-solution of perbenzoic acid in chloroform (50 c.c.), and oxidation allowed to proceed in the dark at room temperature (26°) for 2½ hr. After being washed with 5% sodium hydroxide solution (3×40 c.c.) and then with water (50 c.c.), the chloroform solution was quickly dried (Na_2SO_4) and evaporated at room temperature under reduced pressure. The resulting yellow solid was freed from *trans*-azoxybenzene by trituration with light petroleum (b.p. 40—60°; 3×20 c.c.) and then had m. p. 84° (yield 0·75 g.). Pure *cis*-azoxybenzene, m. p. 87°, was obtained by further trituration with light petroleum (3×20 c.c.) and was identified by direct comparison with a specimen prepared according to Müller and Kreutzmann (*Annalen*, 1932, **495**, 132). Its identity was also confirmed by its conversion into *trans*-azoxybenzene, m. p. 36°, by heating at 100° for ½ hr.

(ii) *trans*-Azobenzene (2·0 g.) was added to a 1·5N-solution of perbenzoic acid in chloroform (30 c.c.), and the resulting solution exposed to sunlight. The flask was cooled by immersion in a beaker of water. After 2 hr., the solution was washed with 10% sodium carbonate solution and dried, and the chloroform evaporated at room temperature. The crude solid remaining was freed from excess of azobenzene and from *trans*-azoxybenzene by washing it with light petroleum (b. p. 40—60°, 5×30 c.c.); the resulting *cis*-azoxybenzene (0·3 g.) had m. p. 86°. On being heated at 100° for ½ hr., it was converted into *trans*-azoxybenzene, m. p. 36°.

cis-m-*Azoxytoluene.*—*cis*-*m*-Azotoluene has been reported as a red oil (Cook and Jones, *J.*, 1939, 1309). In the present work, it was prepared by the method used for *cis*-azobenzene (Hartley, *loc. cit.*) and purified by chromatography. The product solidified on storage at $-5°$ and after recrystallisation from light petroleum had m. p. 46°. By the same procedure as above, it gave *cis*-*m*-azoxytoluene, m. p. 87° on oxidation with perbenzoic acid (Müller and Kreutzmann, *loc. cit.*, give m. p. 89°). When heated at 100° for 1 hr., it was converted into *trans*-*m*-azoxytoluene, m. p. 37°.

cis-p-*Azoxytoluene.*—*cis-p*-Azotoluene was prepared according to Cook's method (*J.*, 1938, 876). It gave *cis-p*-azoxytoluene, m. p. 84°, on oxidation with perbenzoic acid (Müller and Kreutzmann, *loc. cit.*, give m. p. 83—85°). When heated at 100° for 1 hr., it was converted into *trans-p*-azoxytoluene, m. p. 74°.

Reduction of cis-*Azoxybenzene with Lithium Aluminium Hydride.*—A solution of *cis*-azoxybenzene (0·22 g.) in anhydrous ether (20 c.c.) was added dropwise to lithium aluminium hydride (0·3 g.) in ether (15 c.c.) at room temperature. After 1 hr., water (5 c.c.) was added gradually, the reaction mixture filtered, and the ether evaporated. The resulting solid was purified chromatographically by adsorption on alumina from light petroleum. Only one band was obtained. This was washed through, and the solvent evaporated. The *trans*-azobenzene obtained (0·06 g.) had m. p. 68°, unchanged after resolidification.

This work was carried out during the tenure by one of us (G. E. L.) of a C.S.I.R.O. scholarship, for which we express our thanks.

UNIVERSITY OF ADELAIDE. [*Received, January* 14*th*, 1953.]