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THE REARRANGEMENT REACTION OF AZOXYBENZENE WITH ARENESULFONIC ANHYDRIDE

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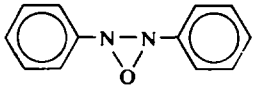
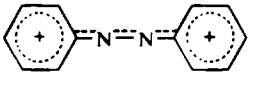
Abstract—Azoxybenzene reacts smoothly with arenesulfonic anhydride to afford *para*-arenesulfonyloxyazobenzene. This rearrangement was found to occur with various substituted azoxybenzenes and arenesulfonic anhydrides. On the basis of ^{18}O and ^{14}C tracer experiments, an intermolecular nucleophilic attack of arenesulfonate ion on the acylated azoxybenzene, after the initial oxygen migration possibly *via* formation of the N, N-oxide intermediate, is conceivable for the course of the reaction. From kinetic observations, especially the effect of the substituents on both the azoxybenzenes and arenesulfonic anhydrides, the N–O bond cleavage is considered to be the rate determining step of the over-all reaction.

AZOXYBENZENE IS KNOWN to rearrange to *p*-hydroxyazobenzene in concentrated sulfuric acid.[1] This acid catalyzed Wallach rearrangement[2] had attracted attention and a substantial amount of mechanistic investigations by means of tracer experiments[3–5] and kinetic observation [6–8] have been carried out. The discussions have mainly focused on the reaction intermediates, i.e., I and II.[9]



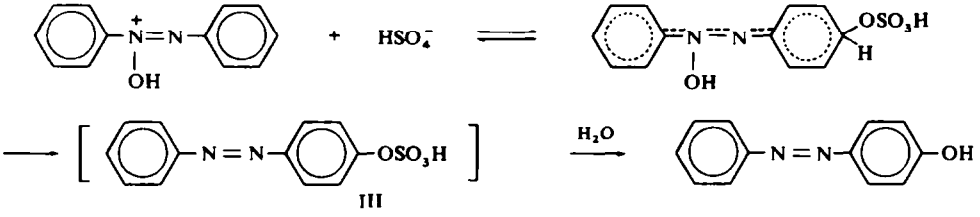
I



II

The prior formation of the N, N-oxide (I) was postulated, because of the observation that hydroxyl group migration takes place at both phenyl groups with equal ease, and oxygen migration from one nitrogen atom to the other actually takes place.[3b] The dication (II) was suggested not only because of the equal ease of migration of the OH group at the two *para* positions of both phenyl groups but also on the basis of kinetic observations.[7]

Recent studies of the Wallach rearrangement,[10–11] suggest that the hydrogen sulfate (III) presumed to be the initially rearranged product, is readily hydrolyzed to the hydroxyazobenzene in the reaction medium as shown below.



III

However, there has been only one report which claims indirect observation of an azoaryl hydrogen sulfate, in very concentrated H_2SO_4, i.e., above 100% H_2SO_4, while the azoaryl hydrogen sulfate has not been isolated in the Wallach rearrangement. Meanwhile, the reaction of pyridine and isoquinoline N-oxides with arenesulfonyl chloride are known to give 3-pyridyl and 4-isoquinolyl arenesulfonates and the initial step of these reactions is believed to be the sulfonylation of the N-oxy function.[12]

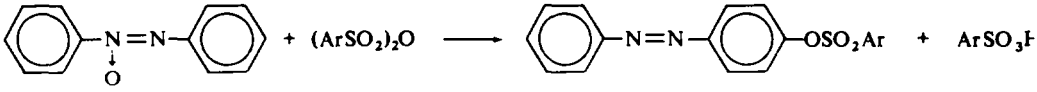
Therefore, if the reaction of azoxybenzene with arenesulfonic anhydride successfully gives the rearranged product, *i.e.*, *p*-arenesulfonyloxyazobenzene, this reaction may lead to an interesting modification of the Wallach rearrangement, because the Wallach reaction and the rearrangement of azoxybenzene with arenesulfonic anhydride have common features, *i.e.*, the generation of a cationic center in the course of the reaction and the subsequent nucleophilic attack of bisulfate or arenesulfonate at aromatic centres.

We have investigated this reaction and now report a new rearrangement affording *p*-arylazo sulfonate, which is very similar to the initially formed product in the Wallach rearrangement, *i.e.*, arylazo hydrogen sulfate.

The product analysis, kinetics, isotopic tracer studies and their implications in the interpretation of the mechanism of the reactions are fully discussed in this paper.

RESULTS AND DISCUSION

Earlier we have shown that the reaction of azoxybenzene with acetic anhydride[13] is sluggish unlike other aromatic and heteroaromatic N-oxides and affords as main products, acetanilide and azobenzene together with tar. Meanwhile, the reaction of a tertiary amine N-oxide with arenesulfonic anhydride has never been investigated. When we allowed azoxybenzene to react with arensulfonic anhydride, however, the reaction proceeded smoothly in either MeCN or C_6H_6 and gave rearranged product, *i.e.*, *p*-arenesulfonyloxyazobenzene along with arenesulfonic acid in nearly quantitative yields.



This is the first example of the rearrangement of a tertiary amine N-oxide with arenesulfonic anhydride. The results are listed in Table 1.

The data reveal that the rearrangement takes place selectively at the *para* position. This implies that after the arenesulfonylation of the azoxy oxygen, the arenesulfonate ion attacks the *para* position of azoxybenzene (considered to be the more electron deficient site[14]) rather than the *ortho* position. The reactions of various substituted azoxybenzenes with *p*-toluenesulfonic anhydride were also carried out and the rearrangement was found to be quite general for various substituted azoxybenzenes. The representative data are summarized in Table 2.

In the case of monosubstituted azoxybenzene, the arenesulfonyloxy group could enter the unsubstituted phenyl ring. In fact, the rearrangement of both α- and β-isomers of 4-bromoazoxybenzene[15] with *p*-toluenesulfonic anhydride yields 4-bromo-4′-(*p*-toluenesulfonyloxy) azobenzene (IV) as the sole rearrangement product.

TABLE 1. THE REACTION OF AZOXYBENZENE WITH *para* SUBSTITUTED BENZENESULFONIC ANHYDRIDE

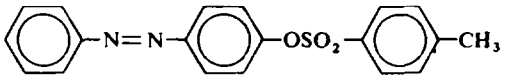
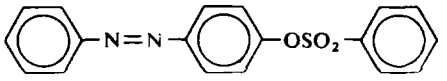
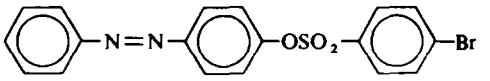
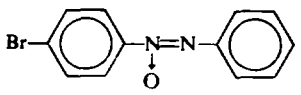
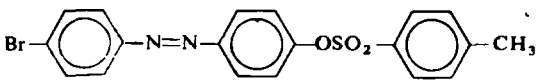
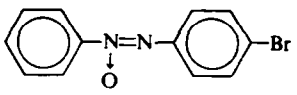
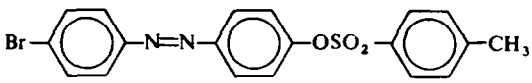
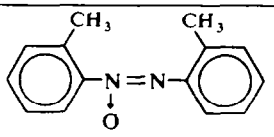
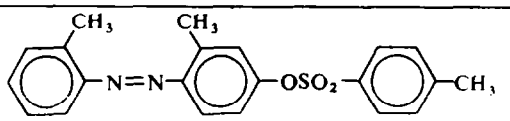
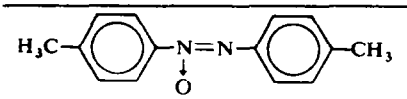
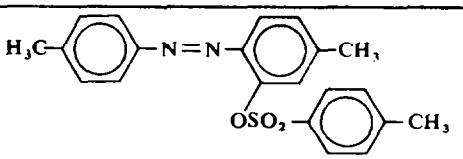
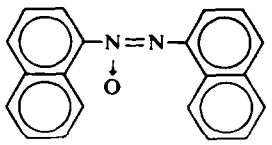
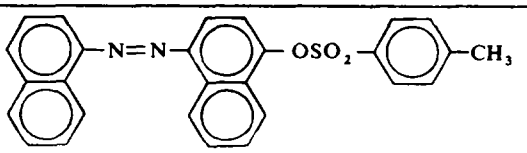
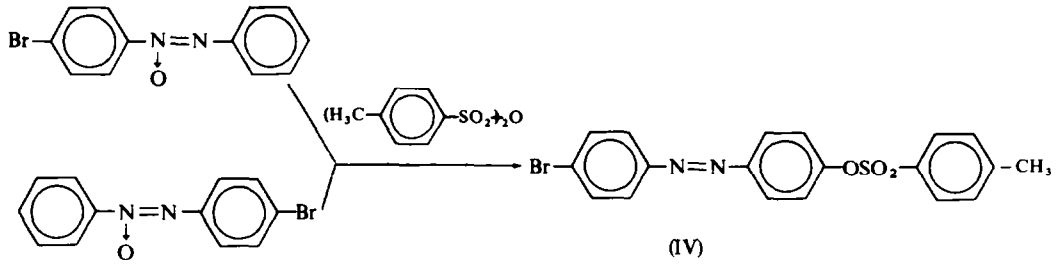
Anhydride	Product	Yield (%)	m.p.
Ts_2O		92	159–60
$(PhSO_2-)_2O$		92	106–7
Bs_2O		86	175–6

TABLE 2. THE REACTION OF SUBSTITUTED AZOXYBENZENE WITH *para* TOLUENESULFONIC ANHYDRIDE

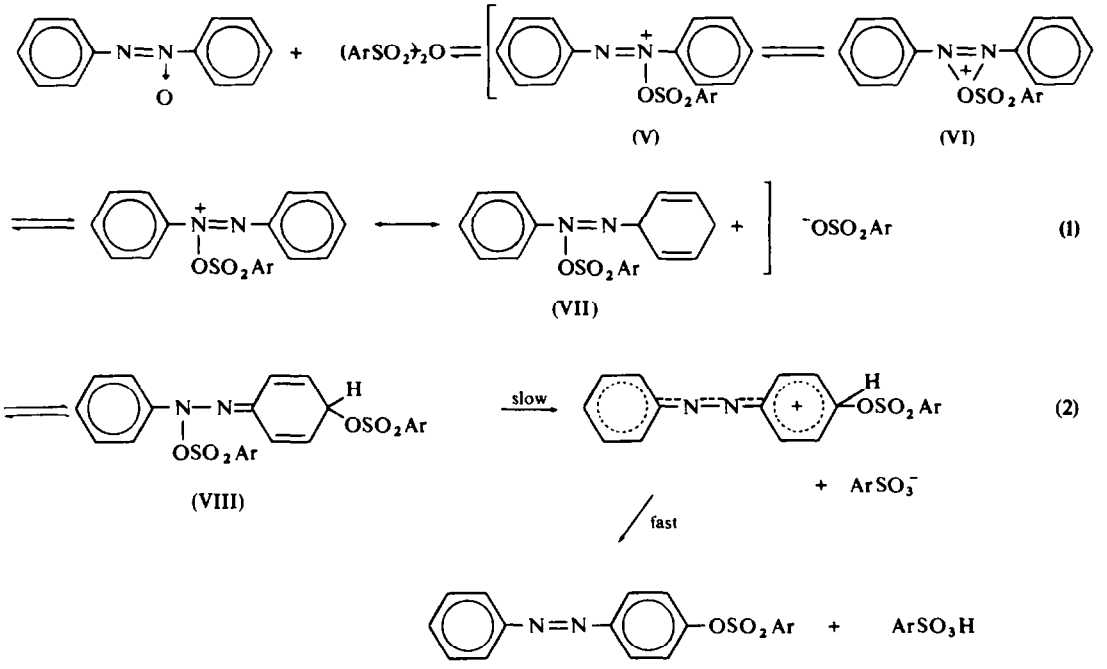
Azoxybenzene	Product	Yield (%)	m.p.
		62	151–3
		75	151–3
		74	92–4
		68	185–7
		70	118–20



(IV)

This suggests that the formation of a structurely symmetrical intermediate such as an NNO ring or the interconversion between α- and β- isomers during the reactions is necessary for the transition state. Another alternative would be the path involving a "dication" intermediate, however, this is rather inconceivable in view of the rather small polar effect by an electron donating substituent as we shall see later. Disubstituted azoxybenzenes were also allowed to react with *p*-toluenesulfonic anhydride in order to clarify the scope and limitations of this rearrangement. Treatment of 2,2′-dimethylazoxybenzene with *p*-toluenesulfonic anhydride gave the *para* tosylated product, while reaction between 4,4′-dimethylazoxybenzene with the same reagent afforded the *ortho* rearrangement product. The results show that these rearrangements occur selectively at the *para* position unless both *para* positions of azoxybenzene are blocked by substitituents. This mode of migration is in strong contrast to that in the reaction of azoxybenzene with arenesulfonyl chloride[16], in which the *ortho* rearranged

SCHEME 1.



(V) (VI)

(VII)

(1)

(VIII)

(2)

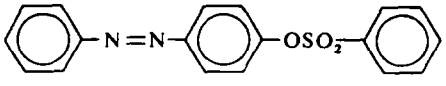
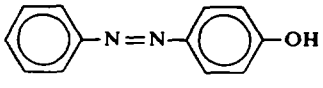
products were obtained along with the *para* rearranged products when an electron-withdrawing group such as NO_2 or Br is substituted on the phenyl ring in benzenesulfonyl chloride. The differences in these two reactions are believed to be due to the different reaction mechanisms as described hereafter. Azoxynaphtalene also rearranges similarly to the *para* position with the same anhydride. The following three successive steps are conceivable for this rearrangement. (1) the sulfonylation of azoxy oxygen, (2) the nucleophilic attack of the arenesulfonyloxy group at the *para* position, and (3) the elimination of the arenesulfonic acid.

The formation of V is reasonable because, in a similar reaction of heteroaromatic N-oxides with Ac_2O, the N-acetoxy salt was actually isolated,[17] while the formation of a similar N-tosyloxy salt was observed in the reaction of isoquinoline N-oxide with tosyl chloride.[18] In the subsequent step, nucleophilic attack of the arenesulfonate is considered to take place and then elimination of arenesulfonic acid as the final stage to give the rearranged product.

^{18}O *Tracer study*

Our usual ^{18}O tracer experiments were carried out with uniformly ^{18}O-labeled benzenesulfonic anhydride to examine the nature of benzenesulfonyloxy migration. The results on the ^{18}Odistribution of the sulfonate and the hydrolyzed product are summarized in Table 3.

TABLE 3. ^{18}O ANALYTICAL RESULTS OF THE REACTION OF AZOXYBENZENE WITH A EQUIMOLAR AMOUNT OF BENZENESULFONIC ANHYDRIDE

Substance	^{18}O excess %
$(PhSO_2-)_2O$	0·61
	0·48
	0·47

Inspection of the data reveals that migration of the benzenesulfonyloxy group proceeds through a completely intermolecular pathway. Namely, when an equimolar mixture of azoxybenzene and uniformly ^{18}O labeled benzenesulfonic anhydride was reacted, the five-sixth excess of ^{18}O is expected to be found in the resulting benzenesulfonyloxy azobenzene in the intermolecular rearrangement. The labeling experiment (0·48) in Table 3 shows this to be true within the experimental error (calculated value: 0·51).

^{14}C *Tracer study*

Another interesting question in this rearrangment is to which phenyl ring, *i.e.*, the

one attached to the N-oxide group or that attached to the azo nitrogen, the arenesulfonyloxy group migrates after the arenesulfonylation of the N-oxy function for the *para* rearrangement.

A ^{14}C tracer experiment was carried out with azoxybenzene-1-^{14}C in order to obtain an information on which ring is subjected to the attack of the sulfonate ion. The location of the ^{14}C was determined by the reductive cleavage of *p*-hydroxyazobenzene with sodium hydrosulfite to *p*-aminophenol and aniline. Aniline was converted to benzanilide, which was then subjected to the usual ^{14}C activity measurements. The degradation scheme is shown below. The results of ^{14}C activity are shown in Table 4.

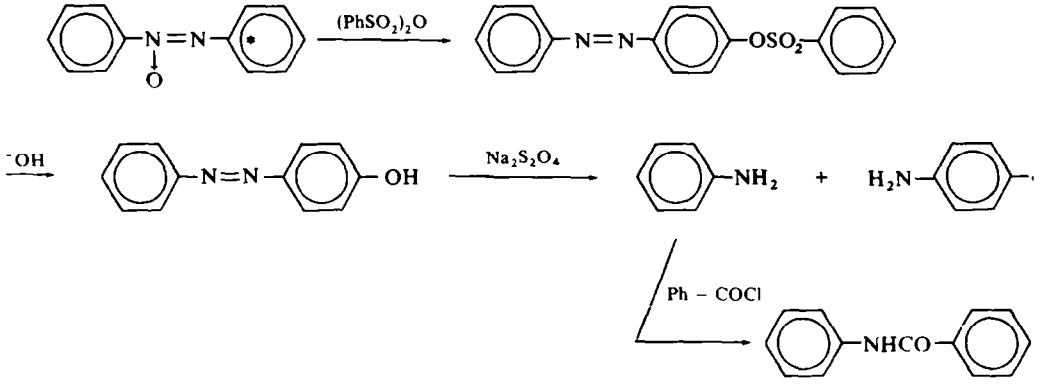
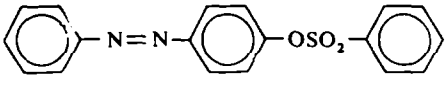
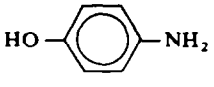
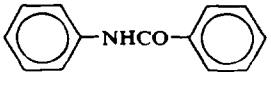
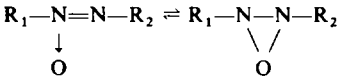


TABLE 4. THE COUNTING DATA OF THE REACTION OF AZOXYBENZENE WITH BENZENESULFONIC ANHYDRIDE

Substance	Activity
	4·85 × 10^4 dpm/m mol
	2·70 × 10^4 dpm/m mol
	1·99 × 10^4 dpm/m mol

The data in Table 4 reveal that attack of the sulfonate was slightly favoured at the phenyl group of the azo side (4-position) compared to the azoxy side (4'-position). This result and the formation of only one identical rearranged product in both cases of α-, β-4-bromoazoxybenzenes show that the main pathway for this rearrangement involves a common intermediate like VI during the course of the reaction. Incidentally,

the photolysis of alkyl azoxy compounds in pentane is known to afford a new three membered ring heterocycle, an oxadiaziridine[19] as shown below.



$R_1 - R_2$ = t-butyl, n-butyl, etc.

Kinetic experiments

To shed further light on the mechanism, a kinetic study of this rearrangement reaction was carried out in MeCN. The rate of the reaction of azoxybenzene with benzenesulfonic anhydride was measured, following the gradual increase of the UV absorption peak at 450 mμ, characteristic of the n-π* transition in the rearranged product. In general the rates were measured in a large excess of benzenesulfonic anhydride and good pseudo-first order rate constants were observed in each case. The order of benzenesulfonic anhydride was determined by changing its concentration and the result is illustrated in Fig. 1.

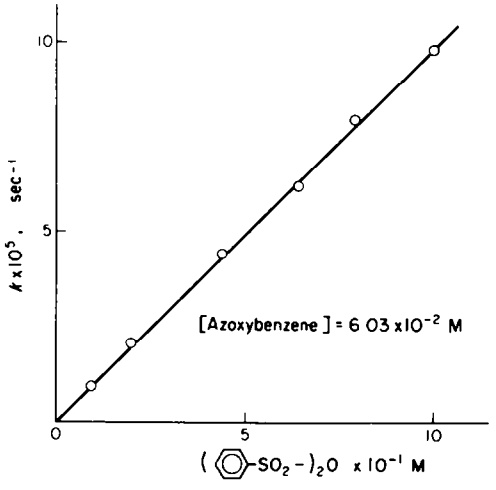


FIG 1

Activation energy (*Ea*) and activation entropy ($\Delta S\ddagger$) are calculated to be 22·4 Kcal/mol and −14·2 e.u. respectively (in MeCN at 60·0°). The large negative activation entropy may indicate that the transition state complex assumes a rigid structure such as VIII in which degree of freedom is considerably lost. Azoxybenzene-d_{10} was prepared by the method of Hendley[10] and subjected to the usual kinetic experiments, practically no kinetic isotope effect (k_H/k_D = 1·00 ± 0·05 in MeCN at 60·0°) was observed. This implies that the rate determining step does not include the loss of a proton from an aromatic ring.

Effect of substituents

The effects of substituents on the substituted benzenesulfonic anhydride were carried out. The kinetic data are listed in Table 5.

TABLE 5. RATE OF THE REACTION OF AZOXYBENZENE WITH SUBSTITUTED BENZENESULFONIC ANHYDRIDE IN ACETONITRILE AT 60·0°

Substituent	10^5k, sec^{-1}	k_{rel}
p-Me_3	1·81	0·61
H	2·96	1
p-Br	6·10	2.06
m-NO_2	20·9	7·06

The results indicate that the rate is increased by an electron-withdrawing substituent such as Br and a considerably large positive Hammett's ρ-value (ρ = 1·3) was obtained. This ρ-value seems to support that the rate determining step could be either the sulfonylation of the azoxy group or the N—O bond cleavage in Scheme 1. The straight line plot of the pseudo first order rate constants against the σ-value is shown in Fig. 2.

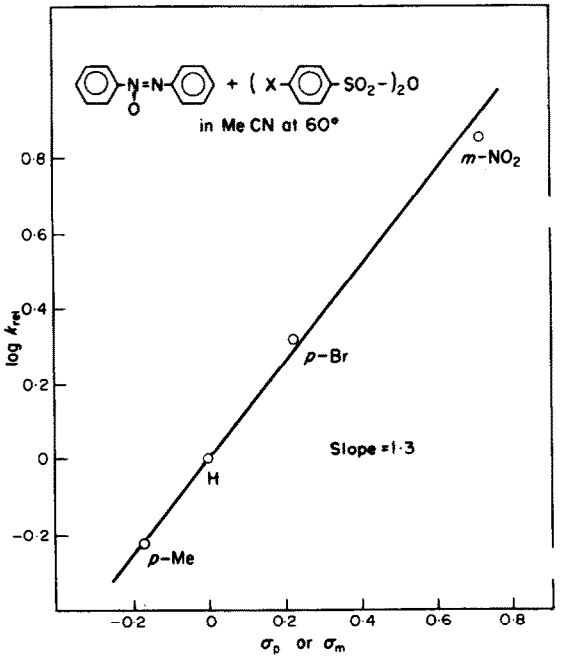


FIG 2. Correlation of the log k_{rel} with Hammett σ value.

The effects of substituents on the α- and β-isomers of the *para* substituted azoxybenzene was also carried out. The kinetic data obtained are listed in Table 6, while the

Hammett plot of the logarithmic rates of 4′-substituted azoxybenzene against σ-values is shown in Fig. 3.

TABLE 6. RATE OF THE REACTION OF SUBSTITUTED AZOXYBENZENE WITH BENZENESULFONIC ANHYDRIDE IN ACETONITRILE AT 60·0°

Substituent	$-pKa^a$	10^5k, sec^{-1}
4′-OMe	6·15	8·16
4′-Me	6·16	4·47
H	6·45	2·96
4′-Cl	6·96	1·42
4′-Br	6·94	1·01
4-Me	6·04	3.55
4-Br	7·01	1·45

[a] These *pKa* values are cited from Ref. 6 written by Hahn and Jaffé.

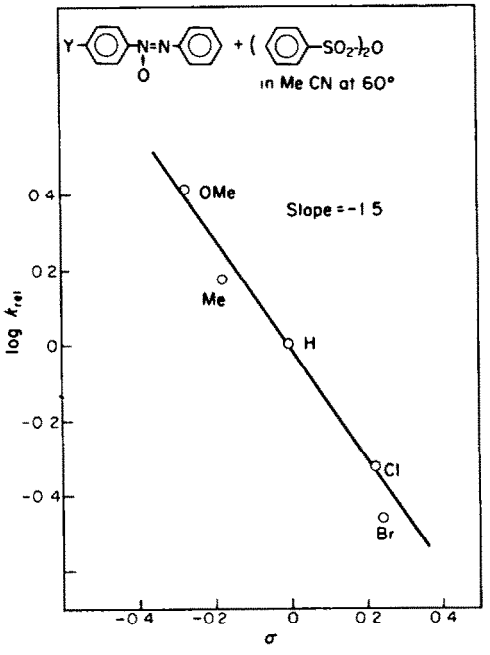
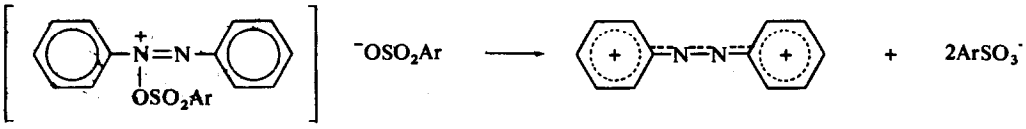


FIG 3. Correlation of the log k_{rel} with Hammett σ value.

These data reveal that the rate is increased by an electron releasing substituent such as OMe and the ρ-value is found to be −1·5. The dication intermediate in Scheme 2 as was considered in the Wallach rearrangement is unlikely in this case since the effect of OMe can be correlated with σ-value but not with σ^+-value.

SCHEME 2



Thus, the large negative ρ-value of the reaction supports that the rate determining step is the N—O bond cleavage in Scheme 1. A question may arise, since the sulfonylation step of the pre-equilibrium reaction (Eq. 1) is also considered to be accelerated by an electron-releasing group in the azoxybenzene. However, this can be ruled out for the following reason. If the sulfonylation of the azoxy group was the rate-determining step, a straight line plot of the rate constants against *pKa* values[6] should be obtained, because the rate should depend linearly on the basicity of the azoxy oxygen. However, the rate constants of the substituted azoxybenzene do not correlate well with the *pKa* values as shown in Table 6. Thus, from the observations of the tracer data and kinetic results, the most plausible mechanism for this rearrangement reaction is considered to be the one involving the rate-determining N—O bond cleavage shown in Scheme 1.

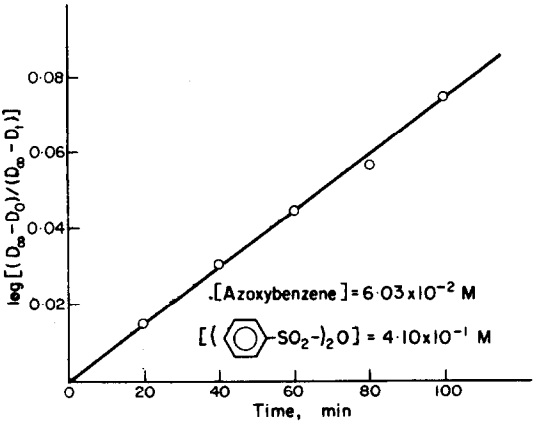


FIG 4.

EXPERIMENTAL

Materials

2,2'-Dimethylazoxybenzene (m.p. 57–9°) was synthesized by the reduction of *o*-nitrotoluene with methanolic NaOH. 4,4'-Dimethylazoxybenzene (m.p. 70–1°) was synthesized similarly. 1,1'-Azoxynaphthalene (m.p. 127°) was synthesized by the oxidation of 1,1'-azonaphthalene with perbenzoic acid.[20] While 1,1'-azonaphthalene was prepared by the action of Na_2SO_3 and NaOAc on diazotised 1-naphthylamine. 4'-*p*-monsubstituted azoxybenzene was synthesized by the reaction of the appropriately substituted azobenzene with H_2O_2 in AcOH. These azoxy compounds were recrystallized from EtOH until m.p.s. became identical to literature values.[6] 4-Methylazoxybenzene (m.p. 46–8°) was synthesized through indazole oxide, according to the method described previously.[21] 4-Bromoazoxybenzene (m.p. 73–4°) was synthesized by the bromination of azoxybenzene with Br_2 in AcOH. Azoxybenzene-d_{10} was prepared by the reduction of nitrobenzene-d_5 with methanolic NaOH.

The deuterium content of azoxybenzene-d_{10} was determined as more than 98% by the comparison of NMR peak areas with that of natural azoxybenzene.

Azoxybenzene-1-^{14}C was prepared by the condensation of *o*-nitrobenzaldehyde with aniline-1-^{14}C in four steps according to the process reported by Behr. Aniline-1-^{14}C was synthesized, starting from barium carbonate-^{14}C, through seven steps. The synthetic method was described previously.[22]

p-Toluenesulfonic anhydride[23] was prepared by the reaction of *p*-TsOH mono-hydrate with P_2O_5 at 125° for 12 hr, while *p*-bromo and *m*-nitrobenzenesulfonic anhydride were synthesized similarly. The properties of these materials were described previously.[24] ^{18}O-labeled benzenesulfonic anhydride was synthesized in the following manner. ^{18}O-labeled benzenesulfonic acid was prepared from the hydrolysis of the ^{18}O-labeled benzenesulfonyl chloride (1·12 excess atom % of ^{18}O) with an excess of ^{18}O-labeled water in dioxane. A mixture of ^{18}O-labeled benzenesulfonic acid (21g) and P_2O_5 (32g) was heated at 120° for 12 hr. After the reaction was completed, the mixture was extracted twice with absolute $CHCl_3$. After evaporation of $CHCl_3$ crude benzenesulfonic anhydride (15g) was recrystallized from absolute ether (m.p. 87–90°). The ^{18}O-analysis was carried out in the usual way.[25]

The reaction of azoxybenzene with arenesulfonic anhydride

A typical run was carried out as follows. Azoxybenzene (0·5 g) and an excess of *p*-toluenesulfonic anhydride (2·0 g) were mixed in MeCN and the mixture refluxed for 2 hr and poured into water The aqueous layer was carefully neutralized with Na_2CO_3, using phenolphthalein as indicator. Then, a 10% ethanolic solution of the S-benzylisothiuronium salt was added to the neutral solution. The precipitate thus formed was collected and recrystallized from EtOH. The crystals (0·9 g, 181–2°) were identified as the thiuronium salt of *p*-TsOH by the comparison with an authentic sample. The oily layer was washed well with water and extracted with $CHCl_3$. After evaporation of solvent, crude *p*- (*p*-toluenesulfonyloxy) azobenzene (0·9 g) thus obtained was recrystallized from EtOH (m.p. 159–60°). This compound was identified by comparison of its properties with those of an authentic sample which was synthesized by treating *p*-TsCl with *p*-hydroxyazobenzene in NaOH aq. The yield was determined by measuring the UV absorption spectra band at 450 mμ in comparison with that of authentic sample. All other reactions were carried out similarly.

^{18}O *Tracer study*

The reactions of azoxybenzene with uniformly ^{18}O labeled benzenesulfonic anhydride were carried out in MeCN. *p*-(Benzenesulfonyloxy) azobenzene (m.p. 106–7°) was obtained by the usual work up, while the hydrolysis of *p*-(benzenesulfonyloxy) azobenzene (0·8 g) was performed in refluxing 20% NaOH aq. for 5 hr. Then the solution was acidified with 10% HCl and extracted with ether. After removal of the solvent, recrystallization from benzene gave *p*-hydroxyazobenzene (m.p. 152–154°, 0·25 g). The results of ^{18}O analysis are summarized in Table 3.

Degradation of p-*benzensulfonyloxyazobenzene*-X-^{14}C

Degradation of the title compound was carried out as previously reported.[16] All compounds were counted with a liquid scintillation counter in toluene solution, using POPOP as the scintillator.

Kinetic runs

The kinetic measurements were performed by following the gradual increase in the UV absorption peak of the rearranged product at 450 mμ, characteristic of the n-π* transition in azo compounds. Good pseudo first order kinetic behavior was observed in each case and a typical run is shown in Fig. 4.

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