Table V. Comparison of Product Ratios and Bond Dissociation Energies

X^a	D_0,[b] kcal mol^{-1}	$\frac{5(1)}{2+3+4}$ [c]
F	109	0.4
CF_3	94	0.5
OH	91	0.7
CH_3	88	1.0
Cl	84	1.5
Br	70	3.2

[a] X in CH_3–X. [b] References 1 and 8. [c] Statistically corrected ratio of yields.

bond strength of the C–X bond in the RF reaction. As shown in Table V, the substituents with weaker bonds are more likely to be lost. The observation (a) suggests that CN prefers to attack at the central, not the terminal carbon atom. This is unexpected on the basis of the extensive literature for radical addition.[13-16,23] It could be explained if the two isomeric radicals **11*** and **12*** interconverted to a small extent before fragmentation. The faster loss of methyl would then bias the product ratios toward **5**. Similarly, (b) could be explained by involving some small amount of rearrangement to give **9***, which rapidly fragmented. Other explanations can, however, be imagined, and clearly, there is not complete equilibration of these activated radicals. If there was, ipso substitution would completely dominate.

Finally, it is of interest in this comparison of photochemistry and RF chemistry to note that RF cyanation using cyanogen is surprisingly cleaner than photolysis using cyanogen. RF also produces more product in a laboratory-scale apparatus and the energy required for RF synthesis is much lower.

Acknowledgment. This work was supported by the National Science Foundation and the Office of Naval Research. Discussions with W. Farneth and D. Johnson are acknowledged.

---

(23) Pryor, W. A. "Free Radicals"; McGraw-Hill: New York, 1966.

Benzidine Rearrangements. 18.[1] Mechanism of the Acid-Catalyzed Disproportionation of 4,4′-Diiodohydrazobenzene. Application of Heavy-Atom Kinetic Isotope Effects

Henry J. Shine,[*†2] **Jan Habdas,**[†] **Harold Kwart,**[‡3] **Martin Brechbiel,**[‡]
Ann Gafney Horgan,[‡] **and Joseph San Filippo, Jr.**[§4]

Contribution from the Departments of Chemistry, Texas Tech University, Lubbock, Texas 79409, University of Delaware, Newark, Delaware 19711, and Rutgers University, New Brunswick, New Jersey 08903. *Received October 25, 1982*

Abstract: Nitrogen and carbon kinetic isotope effects (KIE) have been measured for the two-proton disproportionation of 4,4′-diiodohydrazobenzene (**1**). Disproportionation was carried out in 70% aqueous dioxane under previously described kinetic conditions. The nitrogen KIE was measured by whole-molecule isotope ratio mass spectrometry with the use of mixtures of **1** and [^{15}N,$^{15}N'$]-**1**. The ^{13}C KIE was measured similarly with the use of [4,4′-$^{13}C_2$]-**1**. The ^{14}C KIE was measured by scintillation counting with the use of [4-^{14}C]-**1**. All measurements were made on 4-iodoacetanilide, made after separating the primary products of disproportionation, 4-iodoaniline and 4,4′-diiodoazobenzene. The results were as follows: $k(^{14}N)/k(^{15}N)$, 1.0367 (average); $k(^{12}C)/k(^{13}C)$, 1.0230 (average); $k(^{12}C)/k(^{14}C)$, 1.045. They show that an intermediate is formed with the concerted breaking of the N–N bond and making of a 4,4′-C–C bond. This corresponds with a quinonoid intermediate, proposed earlier by Banthorpe, Cooper, and Ingold.[32] The intermediate subsquently undergoes a rapid redox cleavage reaction with a second molecule of **1**, forming the disproportionation products. The KIE rule out the rate-determining formation of π-complex and radical ion intermediates.

Disproportionation accompanies most acid-catalyzed rearrangements of hydrazoaromatics. In some cases, in fact, disproportionation may be the predominant or sole reaction. The mechanisms of the acid-catalyzed rearrangements have been the source of discussion and controversy for years and only now are being elucidated with the use of heavy-atom kinetic isotope effects.[1,10] One may say with confidence that if the rearrangements have been a puzzle, even more so has been disproportionation.

The stoichiometry of disproportionation is given in eq 1;

$$2ArNHNHAr \rightarrow ArN{=}NAr + ArNH_2 \qquad (1)$$

equimolar amounts of azoarene and arylamine are formed in a reaction which consumes two molecules of hydrazoaromatic. Kinetically, however, the reaction has been found always to be first order in hydrazoaromatic. Furthermore, when disproportionation accompanies rearrangement each reaction has the same kinetic order in acid, whether this be of first,[11,12] second,[13-20] or

---

[†] Texas Tech University.
[‡] University of Delaware.
[§] Rutgers University.

(1) Part 17, *J. Am. Chem. Soc.* **1982**, *104*, 5181.

(2) Supported by the National Science Foundation, Grant No. 8026576.

(3) Supported by the National Science Foundation, Grant No. 7911110.

(4) Supported by the National Science Foundation, Grant No. 8017045.

(5) Shine, H. J. "Aromatic Rearrangements"; Elsevier: New York, 1967; pp 126–179.

(6) Shine, H. J. In "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Interscience: New York, 1969; Vol. 2, pp 191–247.

(7) Banthorpe, D. V. *Top. Carbocyclic Chem.* **1969**, *1*, 1.

(8) (a) Shine, H. J. *MTP Int. Rev. Sci.: Org. Chem., Ser. One* **1973**, *3*, 79–84; (b) *Ibid.: Org. Chem., Ser. Two* **1973**, *3*, 100–110.

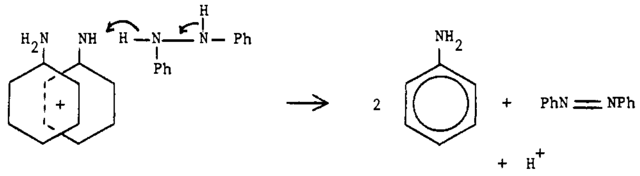
(9) Cox, R. A.; Buncel, E. In "The Chemistry of the Hydrazo, Azo, and Azoxy Groups"; Patai, S., Ed; Wiley: New York, 1975; pp 775–859.

(10) Shine, H. J.; Zmuda, H.; Park, K. H.; Kwart, H.; Horgan, A. G.; Brechbiel, M. *J. Am. Chem. Soc.* **1982**, *104*, 2501.

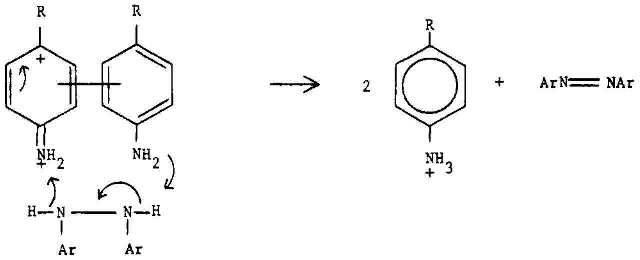
(11) Banthorpe, D. V.; Cooper, A. *J. Chem. Soc. B* **1968**, 605.

0002-7863/83/1505-2823$01.50/0

Scheme I



Scheme II



mixed order.[18,20,21] All investigations of the disproportionation reaction have, therefore, led to the same conclusion, namely, that an intermediate is formed in a pathway that is kinetically identical with that of rearrangement[22] and that the intermediate then oxidizes a second molecule of hydrazoaromatic in a fast step (or steps). The puzzle of disproportionation has been centered on what this intermediate might be. Three possibilities for the intermediate have been proposed in the past and recent literature: a radical or radical ion, a π-complex, and a quinonoid.[24]

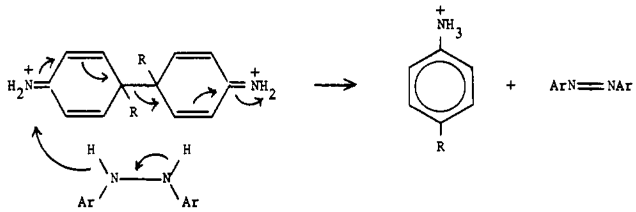
The possibility that a radical or radical ion might be formed in the rate-limiting step (symbolized in eq 2 and 3) and thereafter

$$\mathrm{ArN^+H_2N^+H_2Ar \rightarrow 2ArNH_2^{+\cdot}} \qquad (2)$$

$$\mathrm{ArN^+H_2NHAr \rightarrow Ar\dot{N}H + ArNH_2^{+\cdot}} \qquad (3)$$

oxidize the hydrazoaromatic has been discussed many times. For the most part this possibility has been regarded as either uncertain[15,27] or unacceptable.[12,28-30] On the other hand Hammond and Clovis,[26] in studies with *p*-hydrazotoluene, have concluded that the intermediate in that system must be either the *p*-tolylimino radical (p-$\mathrm{CH_3C_6H_4NH\cdot}$) or its protonated form (p-$\mathrm{CH_3C_6H_4NH_2^{+\cdot}}$). This conclusion stems in part from the finding that an acidified solution of *p*-hydrazotoluene will oxidize other molecules besides *p*-hydrazotoluene, i.e., hydrazobenzene and Würster's base. But, no *certain* evidence for the involvement of radicals or radical ions was obtained in that work; nor has such evidence ever been obtained in any other case of acid-catalyzed rearrangement and disproportionation, in spite of determined searches.[27,28]

Scheme III



The role of a π-complex in disproportionation was first proposed for hydrazobenzene by Dewar when it was believed that its rearrangement was kinetically first order in acid (Scheme I).[31] This idea was then adopted by others for reactions that were second order in acid (Scheme II).[15] There was, of course, no real evidence for the formation of a π-complex or its involvement in any of these reactions.

In 1967 the interesting proposal was made that the intermediate involved in disproportionation had, in fact, a quinonoid structure, much like one which leads to rearrangement.[32] The attractiveness of this proposal was, in part, that it could account for the marked incidence of disproportionation among 4,4′-disubstituted hydrazobenzenes. That is, such a 4,4′-bonded quinonoid, unable to form a benzidine easily by loss of the substituents, was readily available for redox reaction with a second molecule of hydrazoaromatic (Scheme III).

This view has been developed further by Banthrope and Winter in studies with 4-acetamido-, 4,4′-dichloro-, and 3,3′,5,5′-tetrabromohydrazobenzene and their ring-deuterated analogues.[30] From these studies Banthorpe and Winter deduced that while the quinonoids which lead to disproportionation might be 4,4′-bonded in the first two cases (i.e., as in Scheme III), it was unlikely for steric reasons that either 4,4′- or 2,4′-bonded quinonoids could be involved in the last case. They proposed therefore that the most reasonable quinonoid structure was, in fact, the 2,N′-bonded one; i.e., that which corresponds with the formation of an *o*-semidine. Curiously, the fact that an *o*-semidine was *not* formed from 3,3′,5,5′-tetrabromohydrazobenzene was regarded as supportive of the proposal; that is, that the quinonoid intermediate underwent reduction rather than deprotonation (which would have given the *o*-semidine).

In introducing their work Banthrope and Winter noted that despite speculations nothing was known about the mechanism of the disproportionation reaction. They have concluded from their work that "in general rearrangement and disproportionation may be concomitant reactions of different intermediates rather than alternative pathways from a common quinonoid intermediate". Yet, even here, there is no incontrovertible evidence that a quinonoid intermediate *is* involved in the disproportionation reaction.

We have set out to try to distinguish, therefore, among the three possibilities: radical ion, π-complex, and quinonoid. The operational difference between the first two and the last possibilities on which we have focused is in bonding. In order to comply with kinetic findings, an intermediate, regardless of its nature, must have been formed in a rate-determining way. For the forming

---

(12) Banthorpe, D. V.; Cooper, A.; Ingold, C. K. *J. Chem. Soc. B* **1968**, 609.

(13) Vecera, M.; Petranek, J. *Collect. Czech. Chem. Commun.* **1960**, *25*, 2005.

(14) Shine, H. J.; Chamness, J. T. *J. Org. Chem.* **1967**, *32*, 901.

(15) Shine, H. J.; Stanley, J. P. *J. Org. Chem.* **1967**, *32*, 905.

(16) Banthorpe, D. V.; O'Sullivan, M. *J. Chem. Soc. B* **1968**, 615.

(17) Banthorpe, D. V.; Cooper, A. *J. Chem. Soc. B* **1968**, 618.

(18) Banthorpe, D. V.; Ingold, C. K.; O'Sullivan, M. *J. Chem. Soc. B* **1968**, 624.

(19) Banthorpe, D. V.; O'Sullivan, M. *J. Chem. Soc. B* **1968**, 627.

(20) Banthorpe, D. V.; Cooper, A.; O'Sullivan, M. *J. Chem. Soc. B* **1971**, 2054.

(21) Carlin, R. B.; Wich, G. S. *J. Am. Chem. Soc.* **1958**, *80*, 4023.

(22) There is one exception to this statement in the unacceptable speculation on mechanism by Lukashevitch[23] that would require two molecules of hydrazoaromatic to be involved in the rate-determining step.

(23) Lukashevitch, V. O. *Tetrahedron* **1967**, *23*, 1317.

(24) A fourth possibility, a nitrene, has been proposed by Allan.[25] This proposal arose, however, from carrying out reactions of *N*-acetylhydrazobenzene under conditions quite different from the usual ones and from identifying unusual products. Thus, from reaction with concentrated hydrochloric acid small amounts of *o*- and *p*-chloroaniline were detected chromatographically. From reaction in the presence of anisole in 84.5% sulfuric acid, small amounts of 2- and 4-methoxydiphenylamine and aminomethoxybiphenyls were detected. These products were attributed to reactions of phenylnitrene, and the nitrene was also then designated as the oxidant in disproportionation. These reaction conditions are so different from the usual ones that it is not helpful to consider them further here. It is to be noted, also, that Hammond and Clovis had earlier rejected a nitrene as a possible intermediate since it was thought to be unlikely to survive in a hydroxylic solvent.[26]

(25) Allan, Z. J. *Monatsh. Chem.* **1975**, *106*, 429.

(26) Hammond, G. S.; Clovis, J. S. *J. Org. Chem.* **1963**, *28*, 3283.

(27) Vecera, M. Synek, L.; Sterba, V. *Collect. Czech. Chem. Commun.* **1960**, *25*, 1992.

(28) Dewar, M. J. S. In "Kekule Symposium"; Butterworth Press: London, 1958; pp 179–208.

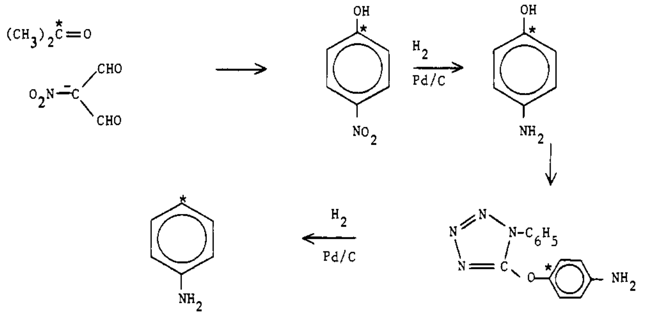
(29) Banthorpe, D. V.; Hughes, E. D.; Ingold, C. K.; Bramley, R.; Thomas, J. A. *J. Chem. Soc.* **1964**, 2864.

(30) Banthorpe, D. V.; Winter, J. G. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 868.

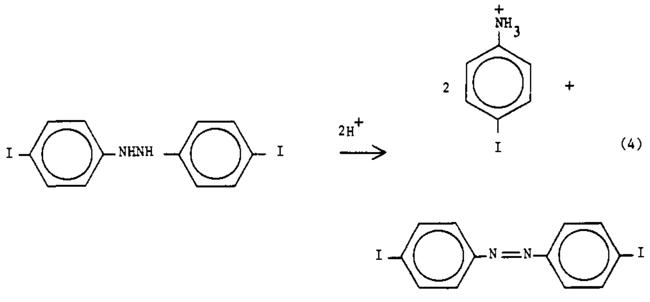
(31) Dewar, M. J. S. "The Electronic Theory of Organic Chemistry"; Oxford University Press: Oxford, 1949; p 239.

(32) Banthorpe, D. V.; Cooper, A.; Ingold, C. K. *Nature* (*London*) **1967**, *216*, 232.

Scheme IV



of a quinonoid structure, therefore, bond formation in an *allowed, concerted reaction* should have a carbon kinetic isotope effect (KIE), whereas the formation of neither the radical ion nor π-complex should be thus characterized. We chose the reaction of 4,4′-diiodohydrazobenzene (**1**) since this was described by Banthorpe and O'Sullivan as undergoing only disproportionation.[19] We assumed further that if a quinonoid intermediate were involved, it would be the 4,4′-bonded one. We sought, therefore, to find whether or not such a quinonoid structure would be formed in a concerted way (i.e., by a 5,5-sigmatropic shift), such as is the one in the formation of benzidine from hydrazobenzene.[10] To do this we made 4,4′-diiodo[^{15}N,^{15}N′]-, 4,4′-diiodo[4-^{14}C]-, and 4,4′-diiodo[4,4′-$^{13}C_2$]hydrazobenzene and measured in each case the KIE for the formation of 4-iodoaniline (eq 4).



(4)

Results and Discussion

Syntheses and Procedures. Labeled 4,4′-diiodohydrazobenzene (**1**) was made as needed from the labeled azobenzene. In each case the appropriately labeled 4,4′-diiodoazobenzene was made (in disappointingly low yields) by the oxidation of 4-iodoaniline with manganese dioxide; the required 4-iodoaniline was made by the direct iodination of the labelled aniline.[33] [^{15}N]Aniline was available commercially. [4-^{14}C]Aniline was obtained by the catalytic hydrogenolysis of [4-^{14}C]azobenzene (approximately 5 mCi/mol) which was available from an earlier study.[10] [4-^{13}C]Aniline was made according to Scheme IV. Although the literature procedure for the condensation of acetone with sodium nitromalonaldehyde records a 74% yield of *p*-nitrophenol after crystallization,[34] we were unable to obtain this yield even as a crude product in many control runs. The 4-nitro[1-^{13}C]phenol was obtained in 69% (crude), and 61.5% yield after purification by column chromatography. Purification was found to be advisable for reduction to 4-aminophenol. In our earlier work [4-^{13}C]aniline was made by hydrogenolysis of the (4-nitrophenoxy)tetrazole (see Scheme IV).[10] In that case the crude [4-^{13}C]aniline was then oxidized to [4,4′-$^{13}C_2$]azobenzene. In the present work it was found that the crude [4-^{13}C]aniline made in this way gave low yields in iodination. Therefore, the purified 4-nitro[4-^{13}C]phenol was first reduced to 4-amino[4-^{13}C]phenol. This procedure was used by Kratzl and Vierhapper,[35] who used a Raney nickel catalyst for the reduction; we found palladium on charcoal to be suitable, even though requiring longer times. Hydrogenation of the 4-(aminophenoxy)tetrazole (Scheme IV) gave [4-^{13}C]aniline, which was isolated as the hydrochloride and converted into 4-iodo[4-^{13}C]aniline.

Table I. Nitrogen and Carbon KIE for the Disproportionation of 4,4′-Diiodohydrazobenzene in 70% Dioxane at 25 °C

% conversion	$k(^{14}N)/k(^{15}N)^{a,b}$	$k(^{12}C)/k(^{13}C)^{a,c}$	$k(^{12}C)/k(^{14}C)$
10	1.0373	1.0230	
10	1.0343	1.0189	
10	1.0387		
15		1.0272	1.045

[a] Results are for doubly labeled molecules. [b] Average of the errors for the three runs, ±0.002. [c] Average of the errors for the three runs, ±0.0058.

Banthorpe and O'Sullivan measured the kinetics of disproportionation of **1** in 60% aqueous dioxane.[19] We found that 4,4′-diiodoazobenzene precipitated from this solvent as the reaction progressed. Our work was carried out, therefore, in 70% aqueous dioxane.

The latter has been described elsewhere by Banthorpe as the slower solvent, and in fact, rates of reaction in 60% were about twice as fast as in 70% aqueous dioxane.[36] We found in working with **1** that this comprison also obtained, so in calculating the times needed for 10% and 15% conversions we used the rate constant for 60% aqueous dioxane[19] and adjusted it by a factor of 2 for 70% aqueous dioxane. Thus, 60 min was allowed for 10% and 95 min for 15% conversion. After the time for conversion had elapsed 40% aqueous sodium hydroxide was added and air was bubbled through the solution overnight to oxidize remaining **1** to the azo compound. The amount of azo compound isolated corresponded well with that anticipated, but the amount of 4-iodoaniline was always somewhat less than anticipated.

Banthorpe and O'Sullivan reported, without giving experimental data, that **1** underwent disproportionation in solutions of sodium hydroxide.[19] We found this to be incorrect. Air oxidation of **1** in alkaline solutions of aqueous dioxane gave 4,4′-diiodoazobenzene quantitatively. Banthorpe and O'Sullivan have also reported that **1** undergoes only disproportionation in acid solutions. TLC showed, however, that the 4-iodoaniline solutions obtained in our workup always contained something with much lower R_f than 4-iodoaniline. We tried but failed to isolate and identify this substance. Because of this problem attempts to isolate or purify the 4-iodoaniline were not made, but instead the crude product was acetylated and the 4-iodoacetanilide was purified and used for isotopic assays.

Kinetic Isotope Effects. The data in Table I show that the disproportionation of **1** is accompanied by both nitrogen and carbon KIE. Bearing in mind that disproportionation is kinetically first order in **1**, the data show, then, that an intermediate is formed in which the breaking of the N–N bond and forming of the 4,4′-C–C bond are concerted. Thus, we can abandon with confidence for the first time the rate-determining formation of both π-complex and radical/radical ion intermediates in this disproportionation reaction. The most reasonable interpretation of the reaction is that a quinonoid intermediate is formed, much in the same way as in the benzidene rearrangement itself,[10] and this, being unable to lose the 4,4′-substituents as easily as in benzidine formation (where they are protons), is reduced rapidly by a second molecule of hydrazo compound (Scheme III). One can allow for the possibility that the quinonoid intermediate, once formed, may break up rapidly into cation radicals which then serve as oxidants of the second hydrazo molecule, but we feel that there is no point in entertaining this possibility seriously.

Experimental Section

Dioxane was distilled over lithium aluminum hydride. Nitrogen gas was passed over heated spun copper to remove oxygen. Silica gel and neutral alumina for column chromatography were respectively from

---

(33) Vogel, A. I. "A Textbook of Practical Organic Chemistry"; Longmans, Green and Co.: New York, 1954; p 619.

(34) Swartz, G. L.; Gulick, W. M., Jr. *J. Labelled Compd.* **1975**, *11*, 525.

(35) Kratzl, K.; Vierhapper, F. W. *Monatsh. Chem.* **1971**, *102*, 224.

(36) Banthorpe, D. V. *J. Chem. Soc.* **1962**, 2407.

Merck (No. 9385, 30–70-mesh ASTM) and Woelm (No. 402135). TLC was carried out with Eastman "Chromagram" silica gel sheets with fluorescent indicator, No. 13181.

4,4′-Diiodo[^{15}N,^{15}N′]hydrazobenzene ([^{15}N,^{15}N′]-1). 4-Iodo[^{15}N]aniline was obtained in 74% yield by iodination of 1.0 g of [^{15}N]aniline.[33] The crude product (1.75 g) was oxidized with freshly prepared manganese oxide[37] to give the crude azo compound in 75% yield. This was purified by column chromatography (alumina, hexane elution) and crystallized from hexane to give 910 mg of 4,4′-diiodo[^{15}N,^{15}N′]azobenzene, mp 241 °C. The unlabeled compound, mp 242 °C,[19] was made similarly from aniline. A mixture of 700 mg of labeled and 13.3 g of unlabeled azo compound was crystallized from 2 L of benzene–hexane (60:40 by volume) and gave 12.7 g of 4,4′-diiodoazobenzene. Mass spectrometry[38] showed the mixture to contain 4.7% of 4,4′-diiodo[^{15}N,^{15}N′]azobenzene. Reduction gave labeled **1** for use in KIE measurements.

4,4′-Diiodo[4,4′-$^{13}C_2$]hydrazobenzene ([$^{13}C_2$]-1). [1-^{13}C]4-Nitrophenol was prepared by the method of Swartz and Gulick.[34] Numerous control experiments gave yields of crude product in the range of 65–70%. A solution of 5.63 g (35.8 mmol) of sodium nitromalonaldehyde monohydrate, 1.0 g (25 mmol) of sodium hydroxide, and 1.7 g (28.8 mmol) of [2-^{13}C]propanone in a total volume of 460 mL of water, standing for 8 days at 2 °C, gave 2.78 g (20.6 mmol, 68.9%) of 4-nitro[1-^{13}C]phenol, mp 106–108 °C. This was purified by column chromatography on silica gel, with chloroform–ethanol (100:1) elution, to give 2.48 g (17.7 mmol, 61.5%) of product, mp 111–112 °C. Purification was necessary, in spite of the loss, because control experiments had shown that subsequent reduction was slow and gave poorer yields unless the nitrophenol was purified.

The 4-nitro[1-^{13}C]phenol was dissolved in 150 mL of ethanol and refluxed with 500 mg of 5% palladium on charcoal and 4.5 mL of hydrazine hydrate (85%) for 1 h. Filtration and evaporation of the solvent gave 1.89 g (17.1 mmol, 97%) of 4-amino[1-^{13}C]phenol, mp 188 °C. Control experiments and TLC showed that the 4-aminophenol prepared by this sequence always had a small impurity. In contrast, when commercial, pure 4-nitrophenol was reduced the impurity did not appear. Nevertheless, the impurity in the synthetic 4-aminophenol did not interfere with further synthesis.

The labeled 4-aminophenol was converted into the 4-aminophenyl ether of 5-hydroxy-1-phenyltetrazole by refluxing for 26 h with 3.2 g (17.7 mmol) of 5-chloro-1-phenyltetrazole and 7 g of anhydrous potassium carbonate in 250 mL of dry acetone and gave 3.34 g (17.1 mmol, 97%) of the ether, [1-phenyl-5-(4-amino[1-^{13}C]phenoxy)tetrazole], mp 169–172 °C. Lit. mp 172–174 °C,[35] 171–173 °C.[39]

Hydrogenolysis of the ether was carried out in 250 mL of benzene in a Parr hydrogenator at 10–15 psi and 35–40 °C with 1.5 g of 5% palladium on charcoal. After filtration and bubbling hydrogen chloride into the filtrate for 15 min a precipitate of 2.07 g (15.9 mmol, 93%) of [4-^{13}C]aniline hydrochloride was obtained. This was iodinated in the usual way and gave after crystallizing from pentane 1.18 g (5.39 mmol, 34%) of 4-iodo[4-^{13}C]aniline, mp 58–61 °C (lit. mp 62–63 °C[33]). Oxidation with manganese dioxide in the usual way gave 4,4′-diiodo[4,4′-$^{13}C_2$]azobenzene, 881 mg (2.03 mmol, 75%) after crystallizing from benzene, mp 242 °C.

A mixture of 800 mg of the labeled and 15.2 g of ordinary azo compound was crystallized from 500 mL of benzene–hexane (5:1) to give 14.8 g of product, mp 247 °C. Mass spectrometry[38] showed that the mixture contained 4.7 mol % of 4,4′-diiodo[4,4′-$^{13}C_2$]azobenzene (mass 436). This material was then reduced as needed to [$^{13}C_2$]-**1**.

4,4′-Diiodo[4-^{14}C]hydrazobenzene ([^{14}C]-1). [4-^{14}C]Azobenzene (approximately 5 mCi/mol) was available from earlier work.[10] A solution of 6.41 g (35.2 mmol) of this in 200 mL of benzene was stirred with 6 g of 10% palladium on charcoal under hydrogen at atmospheric pressure for 20 h. Hydrogen chloride was bubbled into the filtered solution to give 6.21 g (48.0 mmol, 68%) of [4-^{14}C]aniline hydrochloride. The crude hydrochloride was converted into 7.74 g (35.3 mmol, 74%) of 4-iodo[4-^{14}C]aniline. Of this, 7 g (32 mmol) was oxidized without purification to 2.8 g (6.5 mmol, 40.5%) of 4,4′-diiodo[4-^{14}C]azobenzene. This was mixed with an equal amount of oridinary azo compound, and the mixture was crystallized from 3 L of acetone to give 5.2 g of the [4-^{14}C]azo compound, which was reduced to [^{14}C]-^{1} as needed. Reduction gave a mixture of labeled and unlabeled **1** with mp 137–138 °C (lit. mp 137 °C[19]).

Disproportionation of Labeled 1. Several attempts were made to carry out the disproportionation as described by Banthorpe and O'Sullivan in 60% aqueous dioxane (60:40 dioxane-water by volume).[19] However, precipitation of the azo compound occurred during each of these attempts. Therefore, reaction was carried out in 70% aqueous dioxane, as follows. A solution was made of 1.744 g (0.004 mol) of **1** in 500 mL of 70% aqueous dioxane. A second 500-mL solution was made containing 33.2 g (0.312 mol) of anhydrous lithium perchlorate and enough 70% perchloric acid (approximately 16.1 mL) to make the solution 0.376 M in acid. The two solutions were brought to 25 °C under nitrogen and then mixed quickly in a three-necked 2-L flask. The mixed solution was stirred under nitrogen and two 100-mL aliquots were pumped out under nitrogen pressure into calibrated flasks. These aliquots were stored under nitrogen for 24 h and served as the 100% conversion samples. The remaining 800 mL of solution was quenched with 40% aqueous sodium hydroxide after the time calculated for 10% and 15% conversion.

Banthorpe has noted that 70% is a "slower solvent" than 60% aqueous dioxane.[36] We found by measuring conversions that the rate of disproportionation of **1** was about twice as fast in 60% as in 70% aqueous dioxane. Therefore, the times of 10% and 15% conversions were calculated from the rate constant for 60% aqueous dioxane and doubled for the 70% solvent. That is, for 10% conversion we waited 60 min, and for 15% conversion we waited 95 min before quenching the reaction. In any event the conversions were checked by measuring the amount of 4,4′-diiodoazobenzene obtained after workup. Workup involved bubbling air into the quenched, alkaline solution to oxidize the unconverted **1** into the azo compound. The aqueous dioxane solution was then extracted with ether several times, and the combined ether solution was extracted with 5% hydrochloric acid. The ether layer was then worked up to give 4,4′-diiodoazobenzene while the hydrochloric acid layer was neutralized and extracted with ether to give 4-iodoaniline. In these isolations the amount of 4,4′-diiodoazobenzene which was obtained always corresponded well with the calculated anticipated amount, but the yield of 4-iodoaniline was always low and usually in the region of 70%. Furthermore, the 4-iodoaniline was not pure; TLC showed that an impurity was present with lower R_f than 4-iodoaniline. Attempts to purify the product were never wholly satisfactory, and therefore the crude product was acetylated with acetic anhydride and the acetyl derivative was used for KIE measurements. In the ^{15}N and ^{13}C work the 4-iodoacetanilide used for mass spectrometry was recrystallized from aqueous ethanol. In the ^{14}C work the product was not only recrystallized but also sublimed after crystallization.

Banthorpe and O'Sullivan noted that they avoided bringing **1** into contact with strong base solutions (2 N sodium hydroxide) because that caused **1** to disproportionate; but data in evidence were not given.[19] We did not encounter this problem. Had this happened our yields of products from the low conversions could not have been what they were; that is, the action of strong sodium hydroxide solution during air oxidation would have converted **1** into azo compound and arylamine, and our yields of these would have been corresponding low for azo compound and high for arylamine. Furthermore, it was our practice to "recover" unused **1** by oxidizing it with air in alkaline solution to the more storable azo compound. Our recoveries were always good and not troubled by the presence of arylamine which would have been formed had disporportionation in alkaline solution occurred. For example, oxidation of 1.872 g of **1** in 200 mL of 70% dioxane gave 1.809 g (97%) of 4,4′-diiodoazobenzene, mp 242 °C.

Disproportionation of [^{14}C]-1. Runs were made in which the 4-iodo[4-^{14}C]acetanilide from 10% and 100% conversions was compared by scintillation counting after crystallization. However, these runs gave rather high and variable KIE (e.g., 1.14, 1.068, 1.085). Reproducibility was obtained by subliming the product after crystallization. However, in order to obtain enough material for sublimation it was necessary to carry the "low" conversion to an extent of 15%. Thus, 1.744 g (4.00 mmol) of hydrazo compound was used as described above. Workup of the 15% conversion gave 1.29 g (2.96 mmol, 101%) of crude [^{14}C]azo compound and 89 mg (0.206 mmol, 85%) of crude 4-iodo[4-^{14}C]aniline. The 100% conversion gave 91 mg (105%) of crude [^{14}C]azo compound and 69.5 mg (79%) of crude 4-iodo[4-^{14}C]aniline. Each sample of the labeled 4-iodoaniline was acetylated, and the acetyl derivative was crystallized and sublimed at low pressure, giving 4-iodo[4-^{14}C]acetanilide, mp 179 °C. A 2-mg portion of each product in 10 mL of cocktail was counted 10 times and the counts were averaged to give $k(^{12}C)/k(^{14}C)$ = 1.0448. After being kept 1 day the acetyl derivatives were again sublimed and recounted, giving $k(^{12}C)/k(^{14}C)$ = 1.045.

Mass Spectrometer Measurements for KIE. The nitrogen KIE data were obtained by measuring the relative intensities of masses 261 and 262 in the isolated 4-iodoacetanilide and compensating for the relative intensities in unenriched 4-iodoacetanilide. The method and the mass spectrometer have been described earlier.[10] The number of scans made was between 17000 and 37500 for the three sets of samples obtained in three runs. Carbon-13 KIE data were obtained similarly but with the use of a Hewlett-Packard Model 5985 quadrupole mass spectrometer and

---

(37) Wheeler, O. H.; Gonzalez, D. *Tetrahedron* **1964**, *20*, 189.

(38) Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE 68588.

(39) Musliner, W. J.; Gates, W. J., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 4271.

associated data handling system. The number of scans made in each of the three runs was 19 500.

Registry No. 1, 19717-45-4; [^{15}N,^{15}N′]-**1**, 85166-97-8; [$^{13}C_2$]-**1**, 85166-98-9; [^{14}C]-**1**, 85166-99-0; ^{15}N, 14390-96-6; ^{13}C, 14762-74-4; ^{14}C, 14762-75-5; 4-iodo[^{15}N]aniline, 24176-53-2; [^{15}N]aniline, 7022-92-6; 4,4′-diiodo[^{15}N,^{13}N′]azobenzene, 85167-00-6; [1-^{13}C]-4-nitrophenol, 3881-07-0; sodium nitromalonaldehyde, 34461-00-2; [2-^{13}C]propanone, 3881-06-9; [1-^{13}C]-4-aminophenol, 3881-08-1; 1-phenol-5-(4-amino[1-^{13}C]phenoxy)tetrazole, 85167-01-7; 5-chloro-1-phenyltetrazole, 14210-25-4; [4-^{13}C]aniline hydrochloride, 85167-02-8; 4-iodo[4-^{13}C]aniline, 85167-03-9; [4-^{14}C]azobenzene, 81141-91-5; [4-^{14}C]aniline hydrochloride, 85167-04-0; 4-iodo[4-^{14}C]aniline, 85167-05-1; 4-iodoaniline, 540-37-4; 4-iodo[4-^{14}C]acetanilide, 85167-06-2.

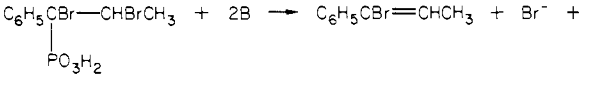
Enol Phosphates from the Action of Monomeric Metaphosphate Ion on Ketones

Kim C. Calvo and F. H. Westheimer*

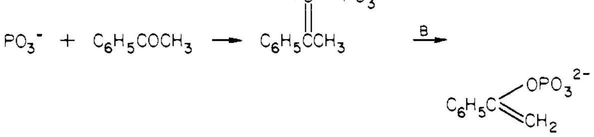
Contribution from the James Bryant Conant Laboratory of the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received June 24, 1982. Revised Manuscript Received November 23, 1982*

Abstract: Prior research from this laboratory had demonstrated that monomeric metaphosphate ion, generated by fragmentation from β-bromophosphonate dianions, reacts with acetophenone in the presence of excess base to give a modest yield of 1-phenylvinyl phosphate. This paper expands on that finding; it presents studies of the effects of concentration of reagents, of solvents, and of variation in amine structure (i.e., of the base) on the reaction. These studies lead to experimental conditions where the yield of the enol phosphate of acetophenone, based on the β-bromophosphonic acid used, exceeds 80%. Several other ketones can be similarly converted to their enol phosphates, although in inferior yield.

The fragmentation of β-bromophosphonate anions[1-3] presumably yields monomeric metaphosphates[4,5] as unstable electrophilic intermediates that can participate in a number of chemical reactions; for methyl metaphosphate,[6] these include aromatic substitution[7,8] as well as the activation of carbonyl groups. Methyl metaphosphate activates acetophenone both toward Schiff base formation and toward enolization to yield methyl 1-phenylvinyl phosphate; it promotes the reaction of ethyl benzoate with aniline to yield *O*-ethyl *N*-phenylbenzimidate. In 1981, Satterthwait and one of us[9] showed that the monomeric metaphosphate anion, PO_3^-, also activates the carbonyl group of acetophenone toward reaction with aniline to form a Schiff base and reacts with the ketone in the presence of excess 2,2,6,6-tetramethylpiperidine (symbolized by "B" in the equations below) to yield 1-phenylvinyl phosphate.



$$C_6H_5CBr(PO_3H_2){-}CHBrCH_3 + 2B \rightarrow C_6H_5CBr{=}CHCH_3 + Br^- + 2BH^+ + PO_3^- \quad (1)$$



$$PO_3^- + C_6H_5COCH_3 \rightarrow C_6H_5C(={}^{+}O{-}PO_3^{2-})CH_3 \xrightarrow{B} C_6H_5C(OPO_3^{2-}){=}CH_2 \quad (2)$$

We postulate that the process takes place by the attack of the monomeric metaphosphate on the carbonyl group of the ketone, as shown in eq 2, and competes with polymerization of metaphosphate for the available phosphorus.

Our view of the mechanism of the process has recently been questioned by Ramirez et al.[10] The present paper records our study of the effects of the concentration of reagents (especially of base), of solvents, of the structure of the base, and of the structure of the ketone on the yield of enol phosphates. Questions of mechanisms are then discussed.

Experimental Section

Materials. (1) ***erythro*- (I) and *threo*- (II) (1,2-dibromo-1-phenylpropyl)phosphonic acids** melted at 188–189 and 181–182 °C, respectively; their spectroscopic properties agreed with those in the literature.[3,8]

(2) (2-Bromo-1,3-diphenyl-3-oxo-1-propyl)phosphonic acid (III) was prepared by the method of Conant and Cook:[2] mp 205–206 °C (lit. mp 196 °C); ^{1}H NMR (CD_3COCD_3) δ 8.28–8.16, 7.70–7.27 (br, m, 10 H), 6.19 (d of d, J_{H-H} = 12 Hz, J_{H-P} = 8.3 Hz, 1 H), 4.31 (d of d, J_{H-H} = 12 Hz, J_{H-P} = 22 Hz, 1 H). Proton decoupled ^{31}P NMR (CD_3COCD_3) δ +17.48 (s). Anal. Calcd for $C_{15}H_{14}BrO_4P$: C, 48.70; H, 3.81; Br, 21.60; P, 8.37. Found: C, 48.82; H, 4.04; Br, 21.46; P, 8.58. The product of the fragmentation of III was identified as *trans*-chalcone by its UV spectrum.[11]

(3) Methyl dihydrogen phosphoric acid showed a proton decoupled ^{31}P NMR peak at δ 1.21 (s). **(4) Anilinium hydrogen 1-phenylvinyl phosphate**[12] melted at 85–86 °C (lit. mp[9] 86.5–87.5 °C). It was converted

---

[1] (a) Conant, J. B.; Cook, A. A. *J. Am. Chem. Soc.* **1920**, *42*, 830. (b) Conant, J. B.; Pollack, S. M. *J. Am. Chem. Soc.* **1921**, *43*, 1665. (c) Conant, J. B.; Coyne, B. B. *J. Am. Chem. Soc.* **1922**, *44*, 2530. (d) Conant, J. B.; Jackson, E. L. *J. Am. Chem. Soc.* **1924**, *46*, 1003.

[2] (a) Maynard, J. A.; Swan, J. M. *Proc. Chem. Soc., London* **1963**, 61. (b) Maynard, J. M. *Aust. J. Chem.* **1963**, *16*, 596.

[3] Kenyon, G. L.; Westheimer, F. H. *J. Am. Chem. Soc.* **1966**, *88*, 3561.

[4] Westheimer, F. H. *Chem. Rev.* **1981**, *81*, 313.

[5] Regitz, M.; Maas, G. *Top. Curr. Chem.* **1981**, *97*, 71.

[6] (a) Clapp, C. H.; Westheimer, F. H. *J. Am. Chem. Soc.* **1974**, *96*, 6710. (b) Clapp, C. H.; Satterthwait, A. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1975**, *97*, 6873.

[7] Satterthwait, A. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1978**, *100*, 3197.

[8] Satterthwait, A. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1980**, *102*, 4464.

[9] Satterthwait, A. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1981**, *103*, 1177.

[10] Ramirez, F.; Maracek, J. F.; Yemul, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1346.

[11] Lutz, R. E.; Jordan, R. H. *J. Am. Chem. Soc.* **1958**, *72*, 4090.

[12] Hata, T.; Yamada, K.; Fututsugi, T.; Sekine, M. *Synthesis* **1979**, 189.

0002-7863/83/1505-2827$01.50/0