Experimental Section

Regular ^{13}C and ^{13}C satellite spectra were recorded at 50.3 MHz on a Varian XL-200 superconducting NMR spectrometer equipped with a variable-temperature broad-band probe.

All the benzonitriles used were commercially available with >99.0% purity and were used as such. Aroyl chloride precursors for benzoyl cation were either commercially available or made by thionyl chloride reaction from the corresponding acids. The acid chlorides were freshly distilled before ionization.

All the benzoyl cations were prepared with use of 1:1 $FSO_3H:SbF_5$ in SO_2 solutions at temperatures of -10 to -20 °C. Solution concentration for the natural abundance coupling constant studies were typically in the order of ~25%.

Similarly ~30% $CDCl_3$ solutions of substituted benzonitriles containing a trace amount of $Cr(acac)_3$ were used at ambient tempeatures for the coupling constant measurements.

The pulse sequence used for the ^{13}C satellite spectra, based on Freeman et al.,[5] is $90°(x)-\tau-180°(\pm y)-\tau-90°(x)-\Delta-90°(\phi)-\mathrm{Acq.}(\psi)$, where $\tau = (2n + 1)/4J_{C,C}$, Δ is a very short delay (~10 μs) needed to reset the radiofrequency phase during which time double quantum coherence evolves, and ϕ and ψ are the phase of the last 90° "read" pulse and the receiver reference phase, respectively. The optimum setting for direct coupling is when $n = 0$ and thus set at 3.1 ms (corresponding to a $^1J_{C,C}$ value of ~80 Hz). The repetition rate of this sequence is 2 and 15 s respectively for benzonitriles [with $Cr(acac)_3$] and benzoyl cations. Reasonable signal to noise was achieved in 6-8 h for the former and in 24-36 h for the latter.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No. **1R** (R = 4-OCH_3), 41868-76-2; **1R** (R = 4-CH_3), 20122-40-1; **1R** (R = H), 19270-10-1; **1R** (R = 4-Cl), 20122-41-2; **1R** (R = 4-Br), 45709-42-0; **1R** (R = 4-F), 39981-36-7; **1R** (R = 3-CF_3), 46060-47-3; **1R** (R = 4-CF_3), 46061-29-4; **1R** (R = 3,5-$(CF_3)_2$), 92270-09-2; **2R** (R = 4-OCH_3), 874-90-8; **2R** (R = 4-CH_3), 104-85-8; **2R** (R = H), 100-47-0; **2R** (R = 3-OCH_3), 1527-89-5; **2R** (R = 4-Cl), 623-03-0; **2R** (R = 4-Br), 623-00-7; **2R** (R = 4-F), 1194-02-1; **2R** (R = 3-CF_3), 368-77-4; **2R** (R = 4-CF_3), 455-18-5; $C_6H_5C{\equiv}CH$, 536-74-3.

Benzidine Rearrangements. 19. The Concerted Nature of the One-Proton Rearrangement of 2,2'-Dimethoxyhydrazobenzene[1,2]

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Abstract: Kinetic isotope effects (KIE) in the acid-catalyzed, one-proton rearrangement of 2,2'-dimethoxyhydrazobenzene (**1**) into 3,3'-dimethoxybenzidine (**2**) have been measured. Nitrogen KIE were determined on the bis(trifluoroacetyl) derivative of **2** which was isolated from low and 100% conversions of mixtures of **1** and [^{15}N,^{15}N']**1** under kinetic conditions. The ratio of masses M(438)/M(436) as determined by whole-ion mass spectrometric techniques led to the result $k(^{14}\mathrm{N})/k(^{15}\mathrm{N}) = 1.0289$ (for two nitrogens). Similar measurements on the derivative of **2** isolated from conversions of mixtures of **1** and [4,4'-$^{13}C_2$]**1** led to the result $k(^{12}\mathrm{C})/k(^{13}\mathrm{C}) = 1.0286$ (for two carbons). These results show that the formation of **2** is a concerted process and, thus, that the acid-catalyzed rearrangement of **1** is a 5,5-sigmatropic shift. Rearrangement via a π-complex intermediate or a solvent-caged, radical/radical-ion pair is excluded. That bonding in the 4,4' positions of **1** is part of the rate-determining step in this rearrangement was confirmed by measurement of an inverse secondary deuterium KIE ($k_H/k_D = 0.929$ for two deuteriums). This result was obtained from ratios of M(244)/M(242) which were measured on 2,2'-dimethoxyazobenzene (**3**), obtained by oxidizing the hydrazo substrate remaining after high conversions of mixtures of **1** and [4,4'-$^2H_2$]**1**.

Acid-catalyzed rearrangement of hydrazoarenes into benzidines, diphenylines, and semidines are called, collectively, benzidine rearrangements. In spite of the very large amount of information which has been gathered about these intramolecular rearrangements,[5-15] questions on their mechanisms still remain. A major mechanistic uncertainty concerns concertedness, that is, whether or not the rearrangements are concerted processes, as described in the polar-transition-state theory of Ingold, Hughes, and Banthorpe,[16] or go through intermediates such as π-complexes[8,9] or solvent-caged radical/radical-ion pairs. Recently we have shown with measurements of kinetic isotope effects (KIE) that the rearrangement of hydrazobenzene into benzidine is a concerted process while the accompanying rearrangement into diphenyline is not.[17] Also, the *p*-semidine rearrangement of 4-methoxy-

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(1) Part 18: Shine, H. J.; Habdas, J.; Kwart, H.; Brechbiel, M.; Horgan, A. G.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 2823.

(2) Taken, in part, from the Ph.D. Dissertation of K. H. Park, Texas Tech University, 1983.

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(4) Rutgers University. Supported by the National Science Foundation, Grant No. CHE 8312730.

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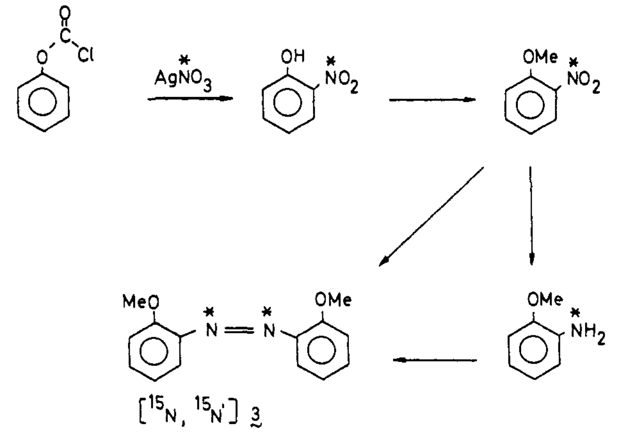
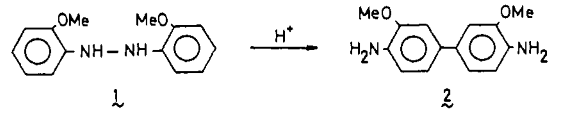
0002-7863/84/1506-7077$01.50/0

Scheme I



hydrazobenzene has been shown to be concerted.[18] Thus, these rearrangements fit the rules of orbital symmetry in sigmatropic rearrangements, and it appears that this should be true of all classes of benzidine rearrangements. One of the characteristics of benzidine rearrangements is that some of them are two-proton while others are one-proton rearrangements. That is, some rearrangements are kinetically second order while others are first order in acid. Reasons for this variation have been given.[16] The prototype of the rearrangements, that of hydrazobenzene, is a two-proton case and we have shown that its conversion into benzidine is concerted. We have wanted to put the test of concertedness to a one-proton rearrangement which also involved 4,4′-bonding, that is, which led to a benzidine-type product. We have now succeeded in this test with the rearrangement of 2,2′-dimethoxyhydrazobenzene (**1**). The kinetics of the one-proton rearrangement of **1** in buffered acidic solutions of aqueous dioxane have been reported by Banthorpe and Cooper.[19] Rearrangement in aqueous ehtanol was found by Croce and Gettler to be too fast to follow,[20a] while the kinetics of rearrangement in aqueous micelle-containing solutions were found to show mixed-acid order by Bunton and Rubin.[20b] We found it convenient, therefore, to use aqueous dioxane solutions as described.[19] Rearrangement of **1** gives one product, 3,3′-dimethoxybenzidine (**2**, eq 1). Therefore our approach to testing for concertedness was to measure the heavy-atom KIE for the formation of **2** in the rearrangements of [^{15}N,^{15}N′]**1** and [4,4′-^{13}C$_2$]**1**. Furthermore, following the approach used in the rearrangement of hydrazobenzene,[17] we set out also to look for an inverse secondary deuterium KIE in the rearrangement of [4,4′-^{2}H$_2$]**1**.



(1)

Results

The experimental plan of our work was to carry out rearrangements of known mixtures of **1** and highly enriched **1** under the kinetic conditions described by Banthorpe and Cooper.[19] Then, by using the rate constants in the literature it was possible to quench a rearrangement at a chosen conversion and to isolate either **2** or unrearranged **1**. Our first objective was to synthesize a labeled 2,2′-dimethoxyazobenzene (**3**) with as much enrichment as possible and to recrystallize a chosen mixture of labeled and unlabeled **3**. The resulting mixture was then reduced to **1** as needed with zinc dust and ammonium chloride.

[^{15}N,^{15}N′]3 was prepared as shown in Scheme I. Silver nitrate was prepared from 99.7% enriched potassium nitrate as the source of ^{15}N. Our intention was to convert the easily made *o*-nitroanisole into [^{15}N,^{15}N′]**3** directly by reduction with zinc and sodium hydroxide. However, a mixture of [^{15}N,^{15}N′]**3** and [^{15}N]-*o*-anisidine was obtained. This mixture was separated and the [^{15}N]-*o*-anisidine was oxidized to labeled **3**. The total yield of [^{15}N,^{15}N′]**3**, after crystallization, was 9.2% based on K^{15}NO$_3$. A mixture of **3** and [^{15}N,^{15}N′]**3** was then crystallized from aqueous ethanol, and the product was found by mass spectrometry to contain 6.3% of [^{15}N,^{15}N′]**3**.

The reaction of phenyl chloroformate with silver nitrate gave *o*-nitrophenyl in 58% yield based on potassium nitrate. This method was chosen because it gives only the ortho isomer. Nitration of phenol with copper nitrate is reported also to give only the ortho isomer.[21] We tried this method but abandoned it because the yields of *o*-nitrophenol were low and variable (27–51%) based on nitrate. Direct nitration of phenol with potassium nitrate in nitric acid[22] was not attractive because of low yields of the ortho isomer and the need for two sources of ^{15}N.

[4,4′-^{13}C$_2$]1 was prepared as in Scheme II. The first 11 of the 16 steps are essentially those described by Kratzl and Vierhapper,[23] for the preparation of [5-^{14}C]guaiacol. We attempted to shorten the procedure for making [4-^{13}C]aniline by hydrogenolysis of both 5-(4-nitrophenoxy)- and 5-(4-aminophenoxy)-1-phenyl-1*H*-tetrazole (**4**), following the original procedure of Musliner and Gates.[24] Hydrogenolysis of the nitrophenyl ether was, in fact, our earlier method of choice.[17] However, each of these methods gave lower yields of aniline than the steps in Scheme II. The conversion of [5-^{13}C]guaiacol (**6**) into labeled *o*-anisidine followed the general procedure of Scherrer and Beatty[25] for the conversion of phenols into anilines via their phenylquinazolyl ethers. Good yields were obtained in most of these steps, although on the whole our yields were not as good as those reported by Kratzl and Vierhapper in the steps toward guaiacol. The poorest of all steps was the last, the oxidation of *o*-anisidine to **3**. Oxidations of arylamines by manganese dioxide usually give very good yields of azoarenes. Notable exceptions are the naphthylamines.[26] However, numerous variations of the general procedure failed to give **3** in higher than 27% yield. The overall yield of [4,4′-^{13}C$_2$]**3** was, therefore, 4.4% based on [2-^{13}C]acetone. We should point out that this acetone, purchased commercially, was 90% enriched. At the time of our work 99% [2-^{13}C]acetone was not available commercially. Therefore, the ^{13}C content of our **3** was destined to be ca. 81% ^{13}C$_2$ and 18% ^{13}C$_1$. Mass spectrometric analysis gave 82.2% ^{13}C$_2$ and 16.8% ^{13}C$_1$. This product was diluted with unenriched **3** and crystallized giving, finally, a mixture of 95.2% **3**, 4.0% [4,4′-^{13}C$_2$]**3**, and 0.77% [4-^{13}C$_1$]**3**.

[4,4′-^{2}H$_2$]3 was prepared as in Scheme III, beginning with commerically available 3-methoxy-4-nitrobenzoic acid. The key product in this sequence of reactions was 3-methoxy-4-nitroaniline, because the succeeding steps were all of well-known reactions. Three other routes to 3-methoxy-4-nitroaniline were tried but were unsuccessful. Thus, attempts at the Schmidt rearrangement[27] of 3-methoxy-4-nitrobenzoic acid failed; starting material was recovered. Nitrosation of *m*-anisidine gave 4-nitroso-*m*-anisidine successfully.[28] But, oxidation of the nitroso group with 30% hydrogen peroxide in acetic acid, a method which has been successful in other cases,[29] failed. Last, nitration of 3-methoxyacetanilide which has been reported to give the 4-nitro derivative,[30-32] gave us only 5-methoxy-2-nitroacetanilide and some unidentified byproducts. Introduction of deuterium into the ring

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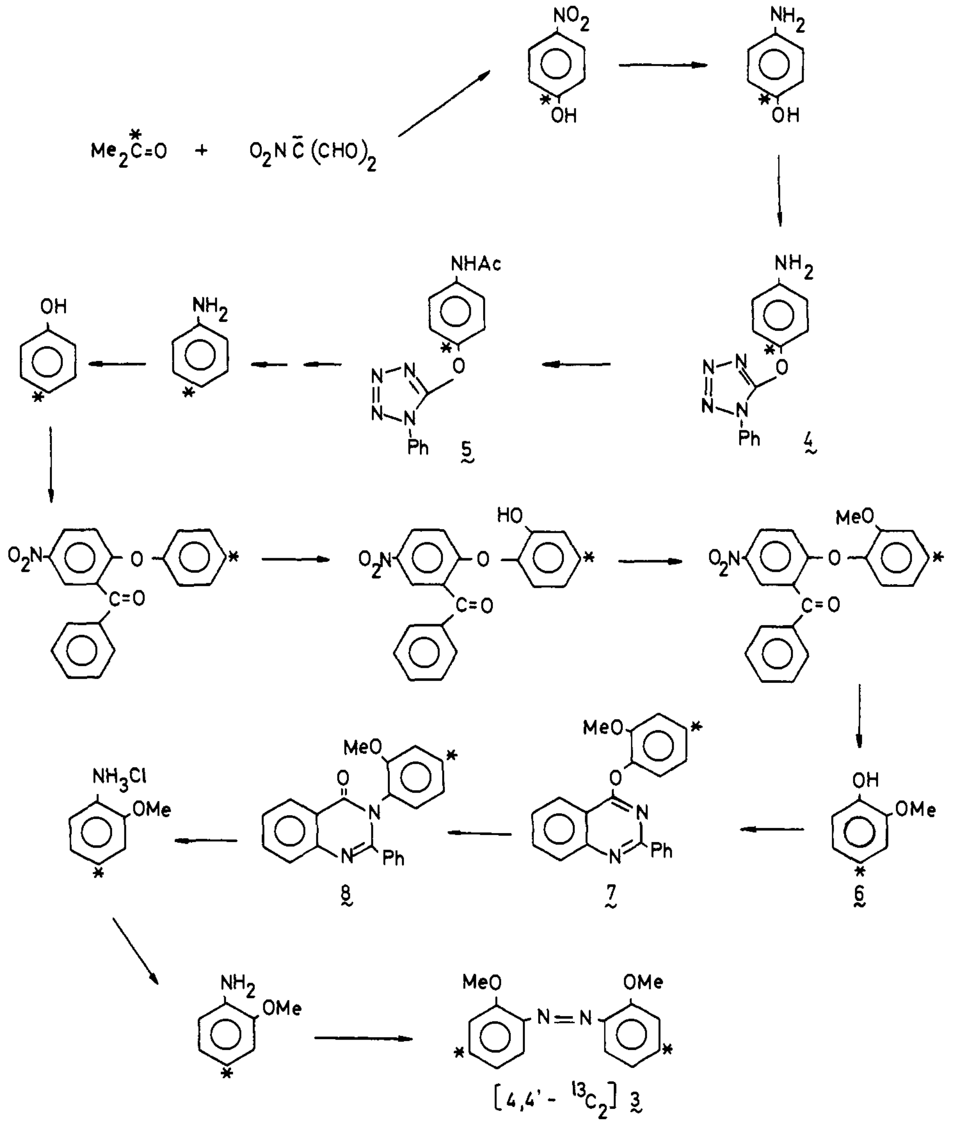
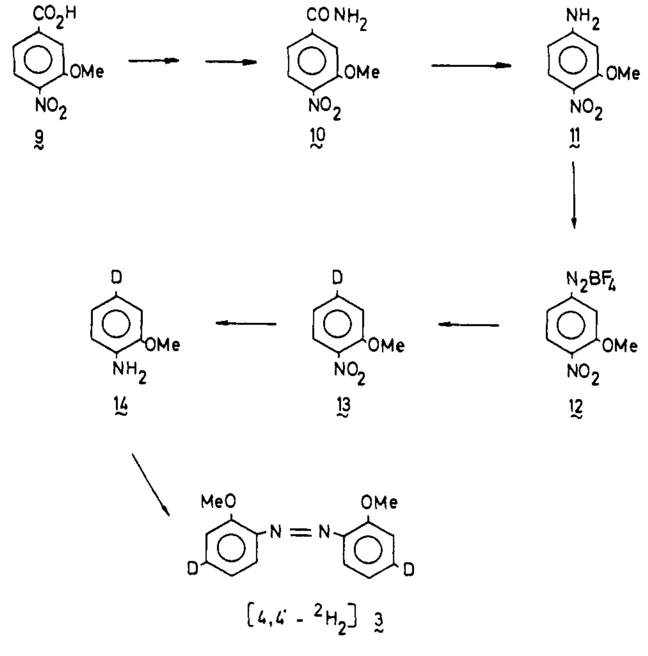
Scheme II



Scheme III



(Scheme III) was achieved with reagents containing 99% deuterium. [4,4'-$^{2}H_{2}$]**3** was obtained in 11% overall yield, but again, all steps gave quite good yields but the last (18%). Dilution of the enriched with unenriched **3** gave finally a mixture containing 3.2% [4,4'-$^{2}H_{2}$]**3** for use in KIE measurements.

Rearrangements are carried out at 0 °C in 60% aqueous dioxane buffered to the prescribed acidity. The procedure for using the chloroacetic acid–sodium chloroacetate buffers is inadequately described in the original literature[19] and was obtained, therefore, from Dr. Cooper's dissertation.[33] Product **2** was isolated at appropriate conversions and, after purification, was converted into its bis(trifluoroacetyl) derivative for mass spectrometry. This derivative was found to be more suitable to our mass-spectrometric measurements than the bis(acetyl) derivative, and it was used so as to avoid our having to make allowances for large (M − 1) abundances which are encountered in the parent compound **2**. Mass ratios M(438)/M(436) were measured at low and 100% conversions. The ratios were normalized to 100% abundance for M(436) and compensated for the natural abundances of the two masses in the product. In calculating the carbon KIE allowance was also made for the portion of M(438) arising from rearrangement of substrate enriched in one ^{13}C atom, M(437), derived from the ^{13}C distribution in the acetone used in synthesis, and amounting to approximately 18% of the substrate. To do this, it was assumed that the ratio of masses M(437)/M(438) was the same as M/(M + 1) of naturally occurring **2**. Also, the KIE for rearrangement of M(437) was neglected. After making all

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Table I. Nitrogen and Carbon Kinetic Isotope Effects in the Formation of 3,3'-Dimethoxybenzidine (**2**) from the Acid-Catalyzed Rearrangement of 2,2'-Dimethoxyhydrazobenzene (**1**)

conversion, %	isotope	k_L/k_H[a,b]
4	^{15}N	1.0238 ± 0.002
15	^{15}N	1.0340 ± 0.0061
2	^{13}C	1.0339 ± 0.0020
4	^{13}C	1.0273 ± 0.0008
14	^{13}C	1.0246 ± 0.0040

[a] For two atoms in [^{15}N,^{15}N']**1** and [4,4'-$^{13}C_2$]**1**. Calculated by the Bigeleisen equation for product.[34] [b] See Experimental Section for calculation of error limits.

Table II. Secondary Deuterium Kinetic Isotope Effect in the Acid-Catalyzed Rearrangement of 2,2'-Dimethoxyhydrazobenzene (**1**)

conversion, %	k_H/k_D[a,b]
37	0.926 ± 0.003
57	0.913 ± 0.001
64	0.924 ± 0.008
77	0.952 ± 0.007

[a] For two deuterium atoms in [4,4'-$^2H_2$]**1**. Calculated by the Bigeleisen equation for reactant.[34] [b] See Experimental Section for calculation of error limits.

compensations, the ratios M(438)/M(436) were used for calculating the nitrogen- and carbon-KIE by the Bigeleisen equation.[34] The results are given in Tabel I.

The procedure for measuring secondary-deuterium KIE was adjusted so as to quench rearrangements at higher (37–77%) conversions and to isolate the starting material in the form of the azo compound (**3**). In these experiments the mass ratios M(244)/M(242) were measured and used for KIE calculations in comparison with the mass ratio of the original azo mixture used in preparing substrate for rearrangement. The results are given in Table II. Part of the workup procedure called for separating **3** from **2** by extracting their ether solution with 5% hydrochloric acid. The total fraction of **3** was subsequently subjected to flash chromatography on silica gel prior to mass-ratio analysis. Therefore, samples of [4,4'-$^2H_2$]**3** were treated similarly and examined mass spectrometrically before and after treatment. Exchange of ring deuterium was not detected.

Discussion

There are substantial nitrogen and carbon KIE in the rearrangement of **1** into **2**. It is evident, therefore, that the breaking of the N–N bond and the forming of the C–C bond are each part of the transition stage of the rearrangement. Thus, this one-proton rearrangement is a concerted, allowed 5,5-sigmatropic shift. The concertedness of the rearrangement should, and does, give rise to an inverse secondary deuterium KIE, associated with the change from sp^2 hybridization at the 4,4'-carbon atoms in **1** to sp^3-like hybridization in the transition state. An inverse secondary deuterium KIE of 3.8% (for two deuterium atoms) was found in the concerted acid-catalyzed rearrangement of hydrazobenzene.[17] In that case, however, two products, benzidine and diphenyline, are formed in 70% and 30% yields, respectively. Because only benzidine formation is concerted and the secondary deuterium KIE was measured (as in the present case) from isotope distributions in the reactant, the real inverse secondary deuterium KIE for benzidine formation is 5.4%. The average value for the formation of **2** is 7.1%. Thus, the two results are of similar magnitudes, and we cannot, at this stage, place any significance on the small difference in the two KIE. The ^{15}N and ^{13}C KIE for the formation of benzidine (1.0222 and 1.0209, respectively) and of **2** (1.0289 and 1.0286) are again of similar magnitudes, and we are reluctant to read any significance into the differences.

The need for only one proton to initiate the rearrangement of certain hydrazoarenes has been ascribed in part to the relative ease with which a unit of positive charge can be delocalized in one of the rings during heterolysis of the N–N bond.[10] Thus, the ease of delocalization is said to enhance heterolysis. In one-proton cases, also, there is no reason to doubt that protonation occurs at nitrogen, rather than at ring carbon, and that this protonation is an equilibrium rather than a rate-determining process.[18] The picture that one sees, therefore, is of N-protonated **1** entering a transition state to rearrangement, of which one-half is aniline-like and the other like a protonated phenylnitrene. It is apparent that in entering this transition state the protonated molecule must have first adopted a configuration in which the two rings are syn to each other rather than anti, as is most probable in unprotonated **1**. The syn relationship is maintained as rearrangement proceeds by the mutual attraction of the two aryl rings, in one of which positive charge and in the other of which a pair of electrons is being delocalized. During C–C bond formation positive charge becomes further delocalized into the aniline-like half of the transition state, just as has been described for the two-proton rearrangement of hydrazobenzene.[18] The transition states for the two rearrangements are, in fact, very much alike, in spite of their differing in proton count. We may, then, view the transition state for rearranging **1** as consisting of two bent, cyclohexadiene-like rings, in which, nevertheless, orbital overlap is maintained.

The rearrangement of **1** thus gives further credence to the growing recognition that benzidine rearrangements are governed by the requirements of orbital symmetry.

Rearrangement of **1** gave **2** exclusively. Although one ortho position is available in each ring of **1** there seems to be no inclination toward forming a diphenyline such as is obtained in 30% yield in the rearrangement of hydrazobenzene. At least if a diphenyline was formed in the rearrangement of **1** it was in too small an amount to be observed in our procedure for isolating **2**. Thus the concerted rearrangement of **1** is dominant. The reason for this behavior remains unknown.

Experimental Section

Materials. Dioxane was distilled over lithium aluminum hydride. Sixty percent dioxane was made by mixing, for example, 60 mL of dioxane and 40 mL of water or aqueous solution. Two buffer solutions were made: I by mixing 80 mL of 1.0 N chloroacetic acid, 4 mL of 1.0 N sodium hydroxide, and 16 mL of water; II by mixing 60 mL of 1.0 N chloroacetic acid, 18 mL of 1.0 N sodium hydroxide, and 22 mL of water.[33] E. Merck 2-mm silica gel plates were used for preparative TLC. Flash chromatography was carried out with 20-μM silica gel from J. T. Baker Co.

[^{15}N,^{15}N']**3**. Ag^{15}NO$_3$ was prepared by mixing a solution of 10 g (98 mmol) of K^{15}NO$_3$ (99.7% ^{15}N, Prochem) in the minimum amount of water with a similar solution of 22.1 g (98 mmol) of $AgClO_4 \cdot H_2O$. The precipitate of KClO$_4$ was filtered and the filtrate evaporated under vacuum. The dried residue was dissolved in 120 mL of dry acetonitrile, and 12.3 mL (98 mmol) of freshly distilled phenyl chloroformate was added dropwise at room temperature under nitrogen. After the mixture was stirred for 5 h the solid inorganic salt was filtered and the filtrate was evaporated in a rotary evaporator. The resulting residue was steam distilled, and 5.6 g (40 mmol) of solid [^{15}N]-*o*-nitrophenol was filtered from the distillate. The distillate was extracted with ether, and the product was purified by preparative TLC. The combined yield of [^{15}N]-*o*-nitrophenol was 8.0 g (58% based on K^{15}NO$_3$). This material was methylated at 100 °C in toluene with dimethyl sulfate,[35] giving crude [^{15}N]-*o*-nitroanisole. This product was reduced with zinc power (8 g) in 100 mL of a 20%, aqueous methanol solution of sodium hydroxide (9.6 g) during 20 h of refluxing. Air was bubbled into the solution to oxidize any hydrazoarene to **3**, and 500 mL of water was added, precipitating 1.6 g of crude **3**. Extraction of the aqueous filtrate with ether gave 3.9 g of [^{15}N]-*o*-anisidine which was oxidized to **3** with activated manganese dioxide.[26] The total yield of [^{15}N,^{15}N']**3** was 2.4 g. Crystallization from aqueous ethanol gave 1.1 g of product (9.2% based on K^{15}NO$_3$), mp 153–155 °C.

[4,4'-$^{13}C_2$]3. Commercial [2-^{13}C]acetone containing 90.6–91.0% ^{13}C was used for preparing [1-^{13}C]4-nitrophenol,[36] which was then converted into [4-^{13}C]2-methoxyphenol ([5-^{13}C]guaiacol (**6**)) essentially as described by Kratzl and Vierhapper for [5-^{14}C]guaiacol.[23] Crude [5-^{13}C]guaiacol (2.0 g, 15.9 mmol), 4-chloro-2-phenylquinazoline (3.7 g,

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15.4 mmol), and 5 g of potassium carbonate were heated under reflux in 90 mL of dry acetone for 41 h. Workup gave 5.1 g (15.4 mmol, 97%) of the crude 2-phenylquinazolyl ether (**7**), mp 102–103 °C. The ether prepared from unlabeled guaiacol had mp 106–108 °C after crystallization from aqueous ethanol. A suspension of the crude, labeled ether in 40 mL of mineral oil was degassed by nitrogen bubbling for 30 min and heated for 9.5 h at 320–325 °C while nitrogen bubbling was continued.[25] This procedure converts the ether (**7**) into the *N*-(*o*-anisyl)quinazolinone (**8**). During exploratory synthesis with unlabeled guaiacol the quinazolinone **8** was isolated and had mp 161–162 °C after crystallizing from ethanol. The same quinazolinone was prepared previously by an entirely different route and had mp 159–160 °C.[37] In the ^{13}C synthesis **8** was not isolated but the thermal rearrangement of **7** into **8** in mineral oil was monitored by TLC until completed. The mineral oil solution was next diluted with 130 mL of ethylene glycol, 10 g of powdered potassium hydroxide and 2 mL of water were added, and the mixture was heated for 12 h at 110–120 °C. After the mixture was cooled to room temperature 90 mL of water was added, and the product was extracted with 1 L of ether. Drying and passing dry hydrogen chloride into the ether solution gave 2.7 g of brown [4-^{13}C]2-methoxyaniline hydrochloride, from which 1.3 g of crude [4-^{13}C]2-methoxyaniline was obtained. After oxidation of this product with manganese dioxide in boiling benzene[26] the crude [4,4′-$^{13}C_2$]**3**, which was obtained, was purified by flash chromatography to give 660 mg, which after crystallization from aqueous ethanol gave 303 mg (1.25 mmol, 27% based on labeled *o*-anisidine) of [4,4′-$^{13}C_2$]**3**, mp 154–155 °C. The overall yield of [4,4′-$^{13}C_2$]**3** based on labeled acetone was 4.4%.

[4,4′-$^2H_2$]3. Commercial 3-methoxy-4-nitrobenzoic acid (**9**, 25 g, 0.127 mol) was converted into its acid chloride with thionyl chloride and thence into the amide (**10**) in quantitative yield, mp 194–196 °C (lit.[38] mp 193–196 °C). Hofmann rearrangement of 22 g (0.112 mol) of **10** was carried out at 85 °C and gave 13 g of crude amine (**11**, mp 155–156 °C) and 5 g of **9**. The amine **11** was purified by reprecipitation from aqueous hydrochloric acid and gave 11.7 g of **11**, mp 159–160 °C. Further purification of **11** was not pursued. Reverdin and Widmer report mp 169 °C for **11** from the nitration of *N*-acetyl-*m*-anisidine;[30] there is some controversy over the products of this and related nitrations.[31,32] Diazotization of 9.9 g (59 mmol) of **11** in a cold solution of boron trifluoride etherate with a solution of *tert*-butyl nitrite in methylene chloride[39] gave 14.9 g (56 mmol, 93%) of the solid diazonium tetrafluoroborate (**12**). This was converted into **13** (8.1 g, 52.6 mmol, 95%) by the general method,[40] and **13** was hydrogenated to the desired 2-methoxy-4-deuterioaniline (**14**) over platinum oxide in benzene. Removal of the benzene gave crude **14** quantitatively, and oxidation of **14** with manganese dioxide gave 4.9 g of crude [4,4′-$^2H_2$]**3**. Chromatography on silica gel gave 2.2 g of what appeared from TLC to be a mixture of the *cis*- and *trans*-[4,4′-$^2H_2$]**3**. Several crystallizations from ethanol gave 1.16 g (18% based on **14**) of [4,4′-$^2H_2$]**3**, mp 152–153 °C. The overall yield, based on **9**, was 11%.

Rearrangements. Just prior to carrying out the rearrangement of **1** an appropriate amount of labeled (diluted) **3** was reduced with powdered zinc and ammonium chloride in acetone. The colorless solution was filtered into aqueous ammonia to precipitate **1** and to keep zinc ions in solution by complexation. The dried **1** was not further crystallized but was used as obtained if its melting point was satisfactory, that is, 102–103 °C (lit[41] mp 101 °C). Occasionally, **1** was obtained with mp 83–85 °C but had the same ^{1}H NMR and IR(KBr) spectra as **1** with mp 102–103 °C. Furthermore, the low-melting product had an acceptable elemental analysis. However, the low-melting product was discarded.

Rearrangement of a weighed amount of **1** was carried out in a solution buffered to a chosen pH. Buffers of dichloroacetic acid were used by Banthorpe and Cooper in rearrangements of **1**.[19] It was necessary for us to use buffers of monochloroacetic acid, however, which were also described by these authors. The compositions of the two buffers which we used are given above. A buffer soltuion was used as described by Cooper[33] and as is given in the examples that follow. In order to know what rate constant should be used the pH of dioxane–buffer trial solutions was measured. The variations in rate constant with pH given by Banthorpe and Cooper were plotted as shown in the original publication[19] but on a larger scale, and this plot was used for extracting rate constants at the pH of the solutions employed in our studies. From these rate constants we determined when to quench a rearrangement reaction for a particular conversion. The times chosen were, however, only a guide as to the conversion, which was, in fact, determined from the amount of product (**2**) obtained or substrate which remained. The latter was measured not as **1**, however, but by the amount of **3** to which the **1** was oxidized after quenching.

Buffer I was used for all deuterium-KIE measurements except that of the 37% conversion, for which buffer II was used. Buffer II was used for all nitrogen- and carbon-KIE measurements. Examples of the procedures follow, first for nitrogen (and carbon) KIE and next for deuterium KIE.

(1) A solution of 1.021 g (4.22 mmol) of [^{15}N,^{15}N′]**1** in a mixture of 600 mL of dioxane and 300 mL of water under oxygen-free argon was cooled in an ice bath to 0 °C. To the stirred solution was added 100 mL of buffer II, precooled to 0 °C. Immediately 150 mL was withdrawn and kept in the refrigerator at 0 °C for 100% conversion. The remaining 850 mL containing 868 mg (3.59 mmol) of **1** was allowed to remain at 0 °C for 90 min, when 50 mL of 40% aqueous sodium hydroxide was added quickly. Air was bubbled gently into the alkaline solution for 24 h to oxidize unrearranged **1**, and the solution was extracted with 5 × 150 mL of ether. The ether solution was next extracted with 5 × 50 mL of 5% hydrochloric acid to remove **2**. The dried ether solution was evaporated and gave 817 mg (3.40 mmol, 95%) of **3**, mp 153–155 °C. The hydrochloric acid solution was made alkaline with solid sodium hydroxide and extracted with 6 × 100 mL of ether. Workup of the ether solution gave 54.7 mg of solid. Flash chromatography on silica with benzene:ether (1500:275 mL) gave 13 mg (1.5%) of **3**, 32.4 mg (0.134 mmol, 3.7%) of **2**, and 4.6 mg of unidentified solid. Compound **2** was crsytallized from water to give 21.2 mg, mp 135–136 °C (lit.[42] mp 138 °C). Of this, 11.4 mg was used make 18.3 mg of the bis(trifluoroacetyl) derivative, which was crystallized from ethanol giving 14.3 mg, mp 235–236 °C. This product was used for mass spectroscopic measurements of the mass ratio M(438)/M(436).

The solution for 100% conversion containing 153 mg (0.632 mmol) of **1** was made alkaline with 30 mL of 40% aqueous sodium hydroxide after several days at 0 °C. The solution was extracted with 4 × 150 mL of ether, and the dried ether solution was evaporated to give 182 mg of solids. Flash chromatography gave 132 mg (86%) of **2** and 12 mg (7.9%) of **3**. In addition, 38 mg of unidentified solids was eluted with acetone. The crude **2** was crystallized and trifluoroacetylated.

Analogous runs were made for the other nitrogen and the carbon KIE. The bis(trifluoroacetyl) derivative of unlabeled **2** was made for normalizing the mass ratio data and had mp 235–236 °C.

(2) To a solution of 500 mg (2.07 mmol) of [4,4′-$^2H_2$]**1** in a mixture of 300 mL of dioxane and 150 mL of water at 0 °C was added 50 mL of buffer I at 0 °C. Quenching after 17.5 h and workup gave 118 mg (0.492 mmol) of **3**, which was crystallized from ethanol, mp 153–154 °C. This product was used for determining the mass ratio M(242)/M(240). The amount of **3** isolated corresponds to 76% conversion of **1**. Analogous rearrangements to 64% (12 h) and 56% (8.75 h) were carried out, giving 180 and 218 mg of **3**, respectively. In the fourth case buffer II was used to reach 37% conversion at a quenching time of 15 h.

For calculating KIE the mass ratio M(242)/M(240) of the starting, labeled **3** was also determined.

KIE Measurements. Mass ratios were determined with a Hewlett-Packard Model 5985B mass spectrometer. All samples were introduced into the mass spectrometer via the solid-sample inlet. Samples were heated as required to maintain a constant source pressure of 8×10^{-7} torr. Data collection was achieved by monitoring the absolute abundances of appropriate ions at 70 eV. A total of 19 950 repetitive scans per sample was obtained with an average dwell time of 50 ms/ion. The resulting data were analyzed in blocks of 750 scans, the absolute abundances being added and then averaged for each block to yield the mean and its standard deviation, from which the ratio of masses was calculated by routine statistical methods. KIE were then calculated from these ratios[34] and are given in Tables I and II. The data in these tables list average errors in KIE. Calculations of the nitrogen and carbon KIE involve the terms $[(M + 2)/M]_{low}$ and $[(M + 2)/M]_{100}$, where low and 100 refer to percent conversion. Calculation of the secondary deuterium KIE involves the terms $[(M + 2)/M]_0$ and $[(M + 2)/M]_{high}$, where zero refers to the starting mixture of **3** and [4,4′-$^2H_2$]**3** and high refers to percent conversion. Standard deviations in abundance measurements were used

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to calculate maximum and minimum measurements of an enriched abundance, i.e., (M + 2) normalized against 100% abundance for M and corrected for the natural abundance of (M + 2) in the mixture. Thus, for each conversion we had eventually a maximum and minimum measure of the enrichment in a sample. Maximum and minimum KIE were calculated from these data and are expressed as an average with its error for each run in the tables.

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Registry No. 1, 787-77-9; **2**, 119-90-4; **2** (bis(trifluoroacetyl) derivative), 92241-72-0; **2**-$^{15}N_2$, 92241-73-1; **3**-$^{15}N_2$, 92241-77-5; **3**-$^{13}C_2$, 92241-86-6; *trans*-**3**-$^2H_2$, 92241-92-4; *cis*-**3**-$^2H_2$, 92241-93-5; **4**, 85167-01-7; **5**, 92241-78-6; **6**, 92241-82-2; **7**, 92241-83-3; **8**, 92269-47-1; **8** (unlabeled), 37856-18-1; **9**, 5081-36-7; **9** (acid chloride), 67579-92-4; **10**, 92241-87-7; **11**, 16292-88-9; **12**, 92241-89-9; **13**, 92241-90-2; **14**, 92241-91-3; ^{15}N, 14390-96-6; ^{13}C, 14762-74-4; D_2, 7782-39-0; $AgClO_4$, 7783-93-9; PhOCOCl, 1885-14-9; $Ag^{15}NO_3$, 92241-74-2; *o*-$HOC_6H_4{}^{15}NO_2$, 92241-75-3; *o*-$CH_3OC_6H_4{}^{15}NO_2$, 92241-76-4; *o*-$CH_3OC_6H_4{}^{15}NH_2$, 63792-03-0; $(CH_3)_2{}^{13}CO$, 3881-06-9; $O_2NC^-(CHO)_2$, 34460-99-6; *p*-HO[4-^{13}C]$C_6H_4NO_2$, 3881-07-0; *p*-HO[4-^{13}C]$C_6H_4NH_2$, 3881-08-1; [4-^{13}C]$C_6H_5NH_2$, 55147-71-2; [4-^{13}C]C_6H_5OH, 70211-36-8; *o*-CH_3O[4-^{13}C]$C_6H_4NH_3Cl$, 92241-84-4; *o*-CH_3O[4-^{13}C]$C_6H_4NH_2$, 92241-85-5; $K^{15}NO_3$, 57654-83-8; 2-[4-^{13}C]phenyl-5-nitrobenzophenone, 92241-79-7; 2-([4-^{13}C]-*o*-hydroxyphenyl)-5-nitrobenzophenone, 92241-80-0; 2-([4-^{13}C]-*o*-methoxyphenyl)-5-nitrobenzophenone, 92241-81-1; 4-chloro-2-phenylquinazoline, 6484-25-9.

Rates and Equilibria of the Reaction of 2,4,6-Triphenylthiopyrylium Ion with Piperidine and Morpholine in Me_2SO. An Unusual Proton Transfer to a Nitrogen Base

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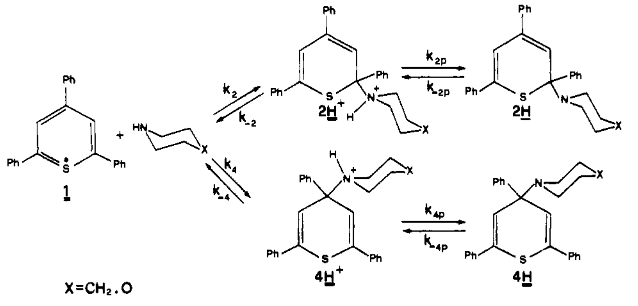
Abstract: The complete set of kinetic and equilibrium constants of the reaction of 2,4,6-triphenylthiopyrylium ion (**1**) with piperidine and morpholine has been obtained in Me_2SO at 25 °C. The reaction involves the formation of both the corresponding 2*H*- and 4*H*-thiopyrans, which equilibrate to form only the more stable 2*H* adduct. The kinetic data are consistent with a two-step process wherein the proton transfer from the protonated 2*H*- and 4*H*-thiopyran intermediates to the amine is the rate-controlling step. The thermodynamically favored proton transfer to the neutral adducts by the solvated proton shows a rate below the diffusion limit, whereas the observed Brønsted coefficient would indicate a diffusion-controlled process. This behavior is discussed in terms of the Eigen mechanism. The factors affecting the nucleophilic addition are discussed, and a comparison is made with the previously reported reaction of **1** with primary amines.

The reaction between nucleophiles and organic cations to yield the corresponding attachment products is a fundamental process in organic chemistry, but in spite of its apparent simplicity the affecting factors are not yet fully understood.[1]

The heteroaromatic cations pyridinium, pyrylium, and thiopyrylium are well suited to obtain insights into these processes. In fact, these ions can be substituted on the two reactive positions, namely the Cα and Cγ carbon atoms, with several substituents having different electronic and steric requirements; moreover, a large number of nucleophiles can react with these substrates making possible the study of the factors affecting both the reactivity and the positional selectivity.

Our interest for these reactions has prompted us to report on a detailed kinetic study of the reaction of 2,4,6-triphenylthiopyrylium ion (**1**) in Me_2SO at 25 °C to yield the corresponding 2*H*- and 4*H*-thiopyrans with piperidine and morpholine, which have different nucleophilicities and identical steric requirements. The aim is to compare this reaction with the corresponding one of the butylamine and cyclohexylamine,[2] in order to study the effect of the structure of the amine on the addition reaction of such a reactive cation.

Scheme I



Results

The kinetic study of the reaction of **1** with piperidine/piperidinium and morpholine/morpholinium buffers, carried out at 410 nm, where only **1** absorbs, and at 355 nm, where both **1** and the 2*H* adduct absorb (Figure 1), showed the presence of two relaxation processes, whose separation increased on increasing the amine/ammonium ratio. Whenever the condition $\tau_1^{-1} \gg \tau_2^{-1}$ was fulfilled (τ_1 and τ_2 are the relaxation times of the first and the second process, respectively), the substrate completely disappeared when the first process was over. Similarly to the primary amine reactions,[2] monitoring the process at 355 nm, an initial decrease

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