Mechanistic Studies of the Fischer Indole Reaction

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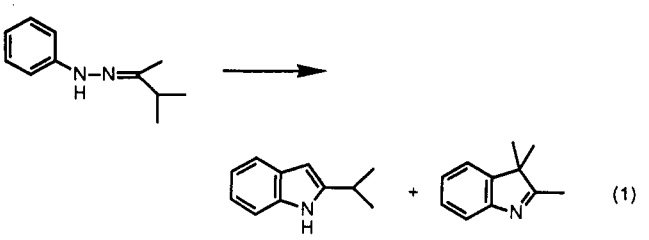
Kinetic and solvent isotope effects were measured for the Fischer indole reactions of four hydrazones. Under neat acid conditions (5% P_2O_5/$MeSO_3H$) the KIE's ranged from 3.2 to 5.8, while the solvent isotope effects (k_H/k_D) ranged from 0.4 to 0.7. Under dilute acid conditions in sulfolane solvent, both isotope effects were near unity. The large kinetic isotope effect and large inverse solvent isotope effect, along with the observation that isotopic exchange occurs in the aromatic ring of the hydrazones, suggest that a preequilibrium protonation of the aromatic ring occurs followed by the rate-determining ene-hydrazine formation under the neat acid conditions. In contrast, under the dilute acid conditions, the lack of isotope effects and the lack of ring isotope exchange indicate that no ring protonation is occurring, that ene-hydrazine formation is no longer rate-determining, and that the rate-limiting step is now most likely the [3,3] rearrangement.

Since its discovery in the 1880's by Emil Fischer, the Fischer indole synthesis has been one of the most versatile and widely used reactions in organic chemistry.[1] Accompanying the numerous synthetic applications of the reaction following its discovery was wide interest in the mechanism. A number of pathways were proposed during the period of 1912–1950, but the one formulated by Robinson and Robinson (Scheme I) in 1924 is now generally accepted.[2] Perhaps because of the early establishment of the reaction pathway, further work on the details of the mechanism of the reaction has been limited over the past three to four decades, although a number of issues have not been adequately explained. Some of these unanswered questions include (1) which step is rate determining, (2) does mono- or diprotonation occur prior to [3,3] rearrangement, (3) does the rearrangement occur concertedly or via intermediates, and (4) what factors govern the regiochemistry when unsymmetrical ketones or 3-substituted arylhydrazones are used in the reaction?

It is likely that the mechanistic details of the reaction depend on reaction conditions and the nature of the hydrazone substrate, so it is doubtful if any definitive mechanism applies to all conditions. In fact, several literature studies suggest that the mechanism changes as conditions are varied. For example, in most indolizations, it is felt that formation of the ene-hydrazine or the [3,3] rearrangement is rate determining, with the later steps being rapid. However, Douglas observed by ^{15}N and ^{13}C NMR buildup of the imine intermediate after the [3,3] rearrangement in the special case where the Nα substituent was an acyl group.[3] Since the resulting amide formed after the rearrangement is a poor nucleophile, the closure of the 5-membered ring then becomes rate determining.

Perhaps more intriguing are the reactions involving unsymmetrical ketones wherein the regiochemistry is completely altered by changing the acidity of the medium, suggesting a change in mechanism. For example, in the cyclization of the phenylhydrazone of isopropyl methyl ketone, Illy and Funderburk[4] found that cyclization from the more branched chain of the ketone resulted at H_0 above −4, while cyclization primarily from the methyl group occurred below H_0 −7, with mixtures of regioisomers occurring at H_0 levels of −4 to −7 (eq 1).



(1)

Many similar examples are reported in the literature.[5] Two theories have been advanced to account for the changes in regiochemistry. Lyle and Skarlos[5e] proposed that steric interactions in the transition state (TS) controlled the regiochemical outcome of the reactions. With small catalysts, such as the proton, minimal steric interactions in the TS would lead to cyclization from the less hindered ene-hydrazine. With larger catalysts, such as Lewis acids, steric crowding would prevent cyclization from the less hindered ene-hydrazine, so instead cyclization would occur via the more thermodynamically stable, more substituted ene-hydrazine. This proposal, however, could not explain differences in regiochemistry observed when the concentration of a single protonic acid is varied. Another proposal was advanced by Palmer and McIntyre,[5a] who suggested that monoprotonation (protonation of the imine nitrogen) occurred in dilute acid and diprotonation (protonation on both nitrogens) occurred in strong acid. According to this theory, in weak acids the formation of the ene-hydrazine is the rate-determining step. This would lead to a TS similar to an E1 reaction in which the ene-hydrazine product would form having the most substituted double bond. On the other hand, diprotonation in very

(1) Robinson, B. *The Fischer Indole Synthesis*; Wiley: New York, 1982.
(2) Robinson, G. M.; Robinson, R. *J. Chem. Soc.* **1924**, *125*, 827.
(3) Douglas, A. W. *J. Am. Chem. Soc.* **1978**, *100*, 6463–6469; *Ibid.* **1979**, *101*, 5676–5678.
(4) Illy, H.; Funderburk, L. *J. Org. Chem.* **1968**, *33*, 4283–4285.
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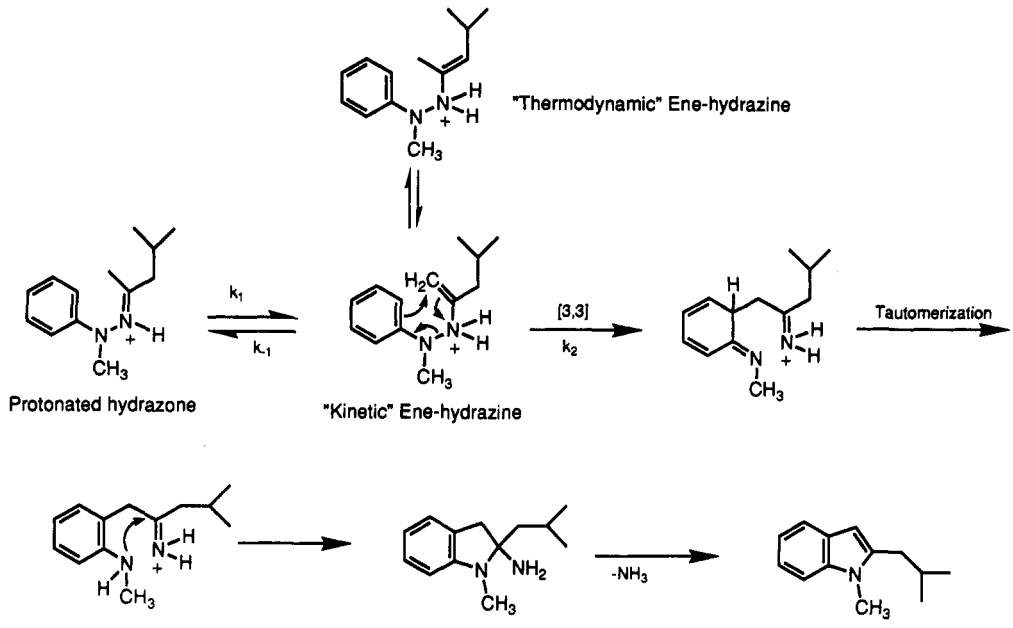
Scheme I



acidic solutions would cause the ene-hydrazine formation to be more E2-like, and therefore the ene-hydrazine having the least substituted double bond would form.

To further probe the mechanistic details behind this unusual change in regiochemistry and to gain further insight into the Fischer indole reaction in general, we have undertaken a study of kinetic and solvent isotope effects in the reaction. We have found that a variation in acid concentration causes a corresponding change in the rate-determining step and is responsible for the change in regiochemistry. In addition, we present evidence that the reaction under strong acid conditions proceeds via aromatic ring protonation, a mechanistic hypothesis not previously postulated for the Fischer indole reaction.

Results and Discussion

We have examined kinetic and solvent isotope effects on the reactions of hydrazones 1–3 and 9 in 5% P_2O_5/$MeSO_3H$ or 5% P_2O_5/$MeSO_3D$ (see Table I for structures) with varying amounts of sulfolane as solvent, as given in Table I. With the symmetrical hydrazones 1 and 9, only one regioisomer is formed. With hydrazones 2 and 3, both regioisomers are formed, with the indole arising from cyclization via the methyl group predominating at high levels of acid, as expected from literature examples. The ratios of regioisomers are the same for the deuterio and protio hydrazones, indicating that a change of D for H does not change the mechanism.

Kinetic Isotope Effects. Kinetic isotope effects (KIE) can be used to determine whether ene-hydrazine formation (k_1 in Scheme I) is rate determining. A substantial KIE would indicate that k_1 is rate determining while a small KIE would indicate a latter step is rate limiting. Only two studies have addressed this question, with conflicting conclusions. In his 1974 review Grandberg[6] concluded that ene-hydrazine formation was rate determining in the Fischer indole reaction based on an isotope effect of 1.8 for the reaction of the phenylhydrazone of cyclohexanone. However, this conclusion was challenged by Jongejan[7] who observed H/D exchange in the indolization of a deuterated hydrazone in formic acid, suggesting that k_1/k_{-1} was a rapid equilibration followed by a slower k_2. For the hydrazones examined here, our data indicate that both conclusions are correct, depending on the reaction conditions. The large isotope effects of 3.5–5.8 (Table I) in the strong acid indolizations clearly indicate that ene-hydrazine formation is rate determining, while the isotope effects near 1.0 in dilute acid indicate that a later step not involving proton transfer is rate limiting. These isotope effects are opposite to what would have been expected from the theory proposed by Palmer and McIntyre,[5a] wherein they had proposed that the rate-determining step would be ene-hydrazine formation in weak acid.

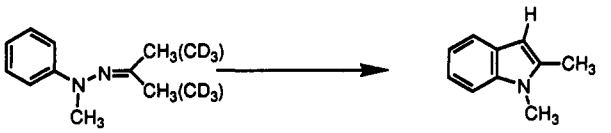
For hydrazone 2, indolizations were carried out in varying ratios of acid to solvent, the solvent in this case being sulfolane. The KIE's drop as the concentration of acid decreases, from a value of 4.2 in neat acid to 1.0 at a 1:25 ratio of acid to solvent. As the acid concentration decreases, the ratio of regioisomers 5:7 also changes. Under the neat acid conditions, primarily regioisomer 5 is formed (12:1 ratio), while under the more dilute conditions, only isomer 7 is formed. Similar results were found with the other hydrazones.

One potential problem with the KIE's measured at the higher dilution, where small isotope effects were observed, is that H/D exchange occurs in the hydrazones before indolization occurs, which would result in the washing out of the KIE. To check on this possibility, the indoles formed from deuterio hydrazones which were run in the protio solvent were isolated at the end of the kinetic experiments to determine if H/D exchange had occurred in the hydrazones. Under the neat acid conditions, minimal exchange (<10%) occurred in the aliphatic portion of the molecules as expected since a high k_H/k_D was found. However, in the dilute acid conditions, exchange was significant. Consequently, rate data in these cases were determined from the first 10% of reaction, before significant exchange could occur. A further check of the

(6) Grandberg, I. I.; Sorokin, V. I. *Russian Chem. Rev.* **1974**, *43*, 115–128.

(7) Jongejan, J. A.; Bezemer, R. P.; Duine, J. A. *Tetrahedron Lett.* **1988**, *29*, 3709.

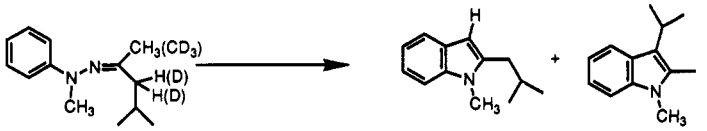
Table I. Rates and Kinetic and Solvent Isotope Effects for Indolization of Hydrazones 1, 2, 3, and 9 in Varying ratios of 5% P_2O_5/$MeSO_3H$ to Sulfolane



1a H_6
1b D_6

4

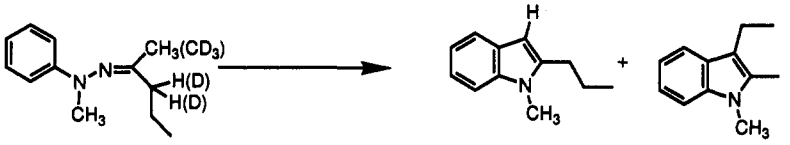
compd	solvent	k, s^{-1} (40 °C)	Kinetic IE (H/D)	solvent IE (SOH/SOD)
1a, protio	neat 5% P_2O_5/$MeSO_3H$	8.84×10^{-5}		0.67
1a, protio	neat 5% P_2O_5/$MeSO_3D$	1.32×10^{-4}	4.56	
1b, deuterio	neat 5% P_2O_5/$MeSO_3H$	1.93×10^{-5}	5.07	0.73
1b, deuterio	neat 5% P_2O_5/$MeSO_3D$	2.62×10^{-5}		



2a H_5
2b D_5

5 **7**

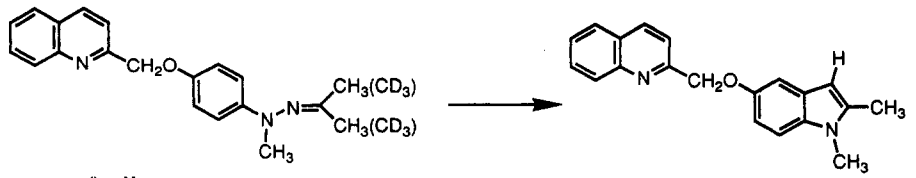
2a, protio	neat 5% P_2O_5/$MeSO_3H$[a]	1.24×10^{-4}	4.2	
2b, deuterio	neat 5% P_2O_5/$MeSO_3H$	2.97×10^{-5}		
2a, protio	neat 5% P_2O_5/$MeSO_3D$	9.93×10^{-4} (60 °C)		0.61
2a, protio	neat 5% P_2O_5/$MeSO_3H$	6.00×10^{-4} (60 °C)		
2a, protio	1:1 5% P_2O_5/$MeSO_3H$–sulfolane[b]	6.75×10^{-7}	4.6	
2b, deuterio	1:1 5% P_2O_5/$MeSO_3H$–sulfolane	1.46×10^{-6}		
2a, protio	1:2 5% P_2O_5/$MeSO_3H$–sulfolane[c]	1.68×10^{-6}	3.3	
2b, deuterio	1:2 5% P_2O_5/$MeSO_3H$–sulfolane	5.10×10^{-7}		
2a, protio	1:5 5% P_2O_5/$MeSO_3H$–sulfolane[d]	1.90×10^{-6}	2.65	
2b, deuterio	1:5 5% P_2O_5/$MeSO_3H$–sulfolane	7.16×10^{-7}		
2a, protio	1:10 5% P_2O_5/$MeSO_3H$–sulfolane[e]	1.15×10^{-5}	2.5	0.87
2b, deuterio	1:10 5% P_2O_5/$MeSO_3H$–sulfolane	4.53×10^{-6}		
2a, protio	1:10 5% P_2O_5/$MeSO_3D$–sulfolane[e]	1.32×10^{-5}	2.3	0.79
2b, deuterio	1:10 5% P_2O_5/$MeSO_3D$–sulfolane	5.70×10^{-6}		
2a, protio	1:25 5% P_2O_5/$MeSO_3H$–sulfolane[f]	7.75×10^{-6}	0.9	
2b, deuterio	1:25 5% P_2O_5/$MeSO_3H$–sulfolane	8.67×10^{-6}		0.93
2b, deuterio	1:25 5% P_2O_5/$MeSO_3D$–sulfolane	9.32×10^{-6}		



3a H_5
3b D_5

6 **8**

3a, protio	neat 5% P_2O_5/$MeSO_3H$[g]	4.72×10^{-5} (35 °C)		0.67
3a, protio	neat 5% P_2O_5/$MeSO_3D$	6.98×10^{-5} (35 °C)	3.17	
3b, deuterio	neat 5% P_2O_5/$MeSO_3H$	1.49×10^{-5} (35 °C)	3.43	0.75
3b, deuterio	neat 5% P_2O_5/$MeSO_3D$	2.03×10^{-5} (35 °C)		
3a, protio	1:10 5% P_2O_5/$MeSO_3H$–sulfolane[h]	6.85×10^{-5} (35 °C)		1.02
3a, protio	1:10 5% P_2O_5/$MeSO_3D$–sulfolane	6.70×10^{-5} (35 °C)	1.73	
3b, deuterio	1:10 5% P_2O_5/$MeSO_3H$–sulfolane	3.95×10^{-5} (35 °C)	1.53	0.91
3b, deuterio	1:10 5% P_2O_5/$MeSO_3D$–sulfolane	4.37×10^{-5} (35 °C)		



9a H_6
9b D_6

10

9a, protio	1:1 5% P_2O_5/$MeSO_3H$	1.13×10^{-5} (60 °C)	5.8	0.56
9a, protio	1:1 5% P_2O_5/$MeSO_3D$	2.00×10^{-5} (60 °C)		
9b, deuterio	1:1 5% P_2O_5/$MeSO_3H$	1.95×10^{-6} (60 °C)	4.3	0.42
9b, deuterio	1:1 5% P_2O_5/$MeSO_3D$	4.67×10^{-6} (60 °C)		
9a, protio	1:10 5% P_2O_5/$MeSO_3H$–sulfolane	2.08×10^{-6} (60 °C)	1.0	1.11
9a, protio	1:10 5% P_2O_5/$MeSO_3D$–sulfolane	1.88×10^{-6} (60 °C)		
9b, deuterio	1:10 5% P_2O_5/$MeSO_3H$–sulfolane	2.10×10^{-6} (60 °C)	1.1	1.27
9b, deuterio	1:10 5% P_2O_5/$MeSO_3D$–sulfolane	1.65×10^{-6} (60 °C)		

[a] Product ratios, 5 to 7: 12:1. [b] 8:1. [c] 3.5:1. [d] 1:25. [e] 1:>500. [f] 1:>500. [g] Ratio of product 6 to 8 was 4:1. [h] Only product 8 was formed.

accuracy of the KIE's was done by running sets of experiments in both the protio and deuterio solvents. For example, the KIE for indolization of hydrazones **2a**/**2b** in 1:10 acid–sulfolane was 2.5 with $MeSO_3H$ and 2.3 with $MeSO_3D$. Since the solvent isotope effects are small, even the comparison of the rate constant of the protio hydrazone in protio solvent (1.15×10^{-5} s^{-1}) vs the rate constant of the deuterio hydrazone in the deuterated solvent (5.70×10^{-6} s^{-1}), wherein no isotopic exchange can occur, gives a similar isotope effect of 2.0. The comparable results of this and the other examples shown in Table I further rule out the possibility of H/D exchange as compromising the results.

The small KIE's at higher acid dilution indicate that k_1 (Scheme I) is no longer rate determining, but that a later step, presumably k_2, is now the rate-determining step. An explanation for the dependence of the regiochemistry on the acid concentration is now possible. Under the strong acid conditions, k_1 is rate determining, so the "kinetic" ene-hydrazine is formed from the less hindered methyl group. As soon as it is formed, it rapidly rearranges and cyclizes to form the indole nucleus (Scheme I). Under the more dilute acid conditions, k_1 is no longer rate determining. Now, there is time for the ene-hydrazines to equilibrate, so the thermodynamically more stable (most substituted) ene-hydrazine is preferentially formed and cyclization from this ene-hydrazine predominates. Although the KIE's clearly indicate a change in rate-determining step is occurring when the acid concentration is altered, the question still remains as to why this change in mechanism is occurring. Product studies and solvent isotope effects shed light no this.

Solvent Isotope Effects. Solvent isotope effects are more difficult to interpret than are kinetic isotope effects, but provide another tool to investigate reactions that can be used with other criteria to support or reject proposed mechanisms. In general, solvent isotope effects are useful in assessing at which stage of a multistep reaction the catalyst (the proton) is involved. Normal isotope effects (SOH > SOD) occur when rate-determining protonation occurs by the solvent (SOH) or protonated solvent (SOH_2^+). An example of this is the acid-catalyzed mutorotation of α-D-glucose, which has reported k_{H_2O}/k_{D_2O} of 1.4–1.9.[8b] On the other hand, inverse solvent isotope effects occur when preequilibrium protonation occurs, followed by a rate-determining step. This is due to weak acids ionizing to a greater extent in D_2O than in H_2O, so that more protonation occurs in D_2O. Another way of saying this is that D_3O^+ in D_2O is a stronger acid than H_3O^+ in H_2O. An example of this is the acid-catalyzed hydrolysis of epoxides which have k_{H_2O}/k_{D_2O} of 0.45–0.55.[8b] In this case, the enhanced rate in D_2O is attributed to a higher concentration of the reactive protonated epoxide in D_2O solution.

The interpretation of solvent isotope effects is further complicated since nearly all literature studies have been done in water or water mixtures. However, sulfuric acid appears to behave similarly to water. Schubert has observed that protonation of aldehydes occurs more completely in D_2SO_4 as compared to H_2SO_4.[9] We assume that the same would apply to $MeSO_3H$ vs $MeSO_3D$.

The inverse solvent isotope effects of $MeSO_3D$ > $MeSO_3H$ (Table I) found with the strong acid conditions are consistent with a preequilibrium protonation step. ^{13}C NMR indicates that monoprotonation of the hydrazones on the sp^2 nitrogen occurs completely with only 2 equiv of $MeSO_3H$ in CD_3CN solution, as the imine carbon moves from 173 ppm in MeCN solution to 191 ppm in the presence of acid. No NMR evidence could be obtained for diprotonation occurring even in neat methanesulfonic acid, so the amount of diprotonation occurring must be small. We observe no solvent isotope effect under the dilute acid conditions wherein the first protonation is occurring. Therefore, the substantial solvent isotope effect measured under the strong acid conditions is consistent with the preequilibrium diprotonation occurring. The inverse solvent isotope effect along with the large kinetic isotope effect is not consistent with the diprotonation step being rate determining, since in that case a normal solvent isotope and no kinetic isotope effect would be expected.

Deuterium/Hydrogen Exchange in the Aromatic Group of the Hydrazones. Product studies for reactions run in $MeSO_3D$ indicated that extensive (>50%) D/H exchange was occurring in the aromatic nucleus of the indole. Since isotopic exchange in the aromatic moiety of indoles has previously been observed in strong acid medium,[10] we suspected that exchange was occurring in the product. However, subjecting indoles **4a** and **5a** to 5% $P_2O_5/MeSO_3D$ gave no H/D exchange in the aromatic ring. Therefore, exchange must be occurring in the starting material or a reaction intermediate. Subjecting hydrazones **1a** and **2a** to the reaction conditions, except at ambient temperature (22 °C) where indolization is slow, demonstrated that exchange was occurring in the aromatic nucleus of the hydrazones, specifically ortho and para to the nitrogen substituent, as expected for electrophilic aromatic substitution for an aromatic ring bearing an electron-donating substituent. Isolation of the product **4a** from the indolization reaction also indicated that only ring exchange had occurred at the positions that had been ortho and para in the hydrazone. Therefore, H/D exchange occurs in the hydrazone and not in any other intermediates along the reaction pathway. The NMR spectra for the hydrazone and indole with interpretation are included in the Experimental Section.

Using the more dilute acid conditions of one part acid to 10 parts sulfolane, no exchange occurs in the aromatic ring of the hydrazone, indicating that no ring protonation occurs.

Mechanistic Hypothesis for the Fischer Indole Reaction. Chart I summarizes the differences between the reactions run in the strong acidic media and those run under the more dilute acid conditions. From these results, we propose the following mechanistic scheme for the reactions of hydrazones that explains the dependence of the regiochemistry on the acid concentration (Scheme II). At a high acid concentration ring protonation (shown as ortho protonation in Scheme II) occurs as an equilibrium step prior to the rate-determining ene-hydrazine formation. This is supported by the studies showing that deuteration of the aromatic ring occurs in the hydrazone at a faster rate than indolization. The inverse solvent isotope effect is also consistent with a preequilibrium

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(10) (a) Bak, B.; Dambmann, C.; Nicolaisen, F. *Acta Chem. Scand.* **1967**, *21*, 1674–1675. (b) Norton, R. S. *Aust. Biochem. Soc.* **1972**, *5*, 18. (c) Norton, R. S.; Bradbury, J. H. *Mol. Cell. Biochem.* **1976**, *12*, 103–111.

Chart I. Summary of Observations in the Fischer Indole Reaction

STRONG ACID CONDITIONS:

Favor kinetic ene-hydrazine formation

Large kinetic isotope effect-- Ene-hydrazine formation is rate-determining step

Large solvent isotope effect--Pre-equilibrium protonation occurs

Aromatic ring deuteration occurs in hydrazone using deuterated acid

• DILUTE ACID CONDITIONS:

Favor more thermodynamically stable ene-hydrazine formation

No kinetic isotope effect--[3,3] rearrangement is probable rate determining step

No solvent isotope effect--no pre-equilibrium protonation

No aromatic ring deuteration of hydrazone using deuterated acid

protonation. The presence of the positive charge in the ring after ene-hydrazine formation, due to ring protonation, leads to rapid [3,3] rearrangement; i.e., k_1 is rate determining and $k_2 > k_{-1}$. This results in cyclization from the least hindered "kinetic" ene-hydrazine. In dilute acid no ring protonation occurs as evidenced by the lack of deuteration in dilute acid and the absence of a solvent isotope effect, so in this case there is no acceleration of the [3,3] rearrangement and it therefore becomes the rate-determining step. Since the [3,3] rearrangement is the slow step, the two isomeric ene-hydrazines have time to equilibrate so that cyclization occurs from the more substituted, more thermodynamically stable isomer.

Comparisons with the Benzidine Rearrangement. The Fischer indole reaction is mechanistically similar to the benzidine rearrangement in that both are sigmatropic rearrangements involving breaking of an N–N bond. In contrast to the limited physical organic chemistry that has been carried out on the Fischer indole reaction, the benzidine rearrangement has been the source of in depth studies and controversy over the past 40 years.[11] Therefore, it is instructive to compare and contrast the results in the literature on this rearrangement with our results with the Fischer indole reaction. From kinetic studies it is known that the benzidine reaction can occur by a one-proton or two-proton mechanism. The first protonation is certainly on nitrogen, while the second has been postulated to be on either nitrogen or an aromatic ring

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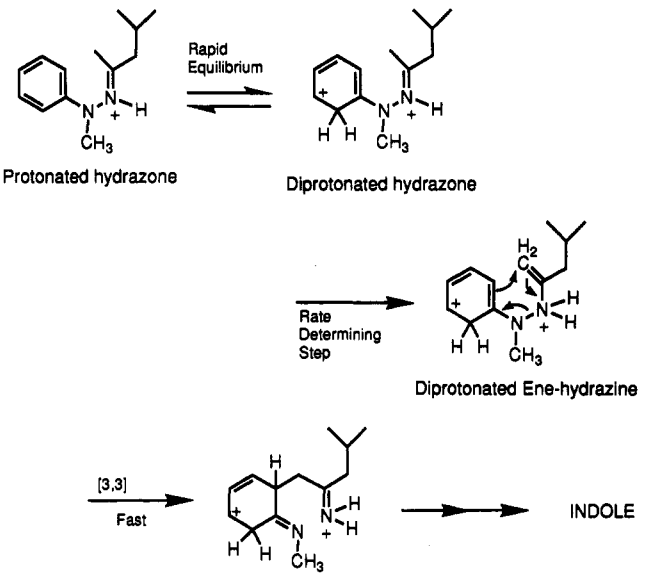
Scheme II



carbon.[12] Olah was a strong proponent of the ring protonation theory, arguing that positive charges on adjacent nitrogens would be disfavored. Shine and co-workers have dismissed this theory since they could find no trace of deuterium incorporation in the aromatic ring when the reactions were run in deuterated acid solvents.[11c,13] Thus, in benzidine rearrangements which involve diprotonation, the current data support protonation on each of the adjacent nitrogens. In Fischer indole reactions, the situation is more complicated since a tautomerization must preceed the [3,3] rearrangement, and we have seen that the tautomerization is rate limiting under strong acid conditions. This results in unusual kinetic orders in acid, a discussion of which is outside the scope of this paper. However, the other data support a diprotonation occurring under strong acid conditions. In contrast to the benzidine rearrangements, however, we find deuterium incorporation in the aromatic ring, giving support for the hypothesis of ring protonation. This ring protonation could be a side reaction that is not on the reaction path, with second protonation of the nitrogen still being the favored reaction pathway for indolization under strong acid conditions. Ways to further distinguish the site of protonation and further mechanistic details of the indole reaction are subjects of current work.

Experimental Section

Preparation of P_2O_5/$MeSO_3H$ Solutions. Commercial methanesulfonic acid (Aldrich) contains 0.3–1% water. It was dried by addition of toluene and atmospherically distilled, as follows. Methanesulfonic acid (20 g, 1.0 wt % water based on Karl Fischer titration) was added to 150 mL of toluene, and the two-phase mixture was distilled to remove the toluene/water azeotrope. The water level dropped to 0.3%. The acid was then distilled at 2 mm, 135 °C, to provide material having a water content of 0.15%. To the distilled acid (8.4 g) was added 420 mg of P_2O_5, and the mixture was stirred for 20 h at ambient temperature to completely dissolve the solid.

(12) (a) Olah, G. A.; Dunne, K.; Kelly, D. P.; Mo, Y. K. *J. Am. Chem. Soc.* **1972**, *94*, 7438–7447. (b) Allan, Z. T. *Tetrahedron Lett.* **1971**, 4225–4228. (c) Allan, Z. T. *Monatsh. Chem.* **1975**, *106*, 429–436. (d) Allan, Z. T. *Liebigs Ann. Chem.* **1978**, 705–709. (e) Lupes, M. E. *Rev. Roum. Chim.* **1972**, *17*, 1253–1260. (f) Heesing, Z.; Schinke, U. *Chem. Ber.* **1977**, *110*, 3319–3323.

(13) Shine, H. J.; Zmuda, H.; Park, K. H.; Kwart, H.; Horgan, A. G.; Brechbiel, M. *J. Am. Chem. Soc.* **1982**, *104*, 2501–2509.

Preparation of $MeSO_3D$. This material was either purchased from Merck Isotopes or made by reacting exactly 1.0 mol of 100% D_2O with freshly distilled methanesulfonic anhydride at 50 °C. The D/H ratio was determined by ^1H NMR.

Preparation of Deuterated Ketones. The deuterated ketones required for making the deuterated hydrazones were made by exchanging the protio ketones in basic D_2O according to the House procedure.[14] A representative procedure for methyl isobutyl ketone (MIBK) is given below. MIBK (5.13 g) was added to 20 mL of D_2O and 80 mg of sodium carbonate and warmed to 60 °C for 18 h. The mixture was cooled, and the layers were separated. The top layer contained 4.73 g of 80% exchanged MIBK, as indicated by ^1H NMR. The process was repeated two more times to give 3.3 g of material of >99% deuterium incorporation. The material was used as is in the preparation of the hydrazones.

Preparation of Hydrazones. The hydrazones were made from the appropriate ketone and hydrazine as described earlier.[15] A representative example for making deuterated hydrazone **2b** is given below. 1-Methyl-1-phenylhydrazine (3.00 g, 24.6 mmol) was added to 10 mL of MeOD and concentrated to an oil. The procedure was repeated twice more to exchange the NH protons of the hydrazine. To the deuterated hydrazine was then added toluene (10 mL), 4-Å sieves (1.3 g), acetic acid-d_1 (3.03 g, 49.7 mmol), and methyl isobutyl ketone-d_5 (2.80 g, 26.7 mmol). The mixture was stirred for 2 h at ambient temperature, filtered, and concentrated to an oil. Toluene (3 × 10 mL) was added to the oil and concentrated to remove the remaining acetic acid. The oil was distilled at 1 mm, 96–98 °C, to provide 3.88 g of hydrazone. ^1H NMR indicated 98% deuterium incorporation.

Kinetic Experiments. The rates of reaction were measured by quantitative HPLC analysis of starting material and products in aliquots of reaction samples. The temperature of reaction was held constant by submerging the reaction vessels in a stirred oil bath which was held constant to ±0.2° by using a Thermowatch temperature controller. The data points were fitted to a first-order kinetic equation, and plots of $\ln A_o/A$ vs time were linear with R^2 values >0.995 for 3 half-lives in all cases wherein no H/D exchange was occurring. In cases where H/D exchange occurred, plots were curved, so the rate constants were obtained from data from the first 10% reaction, where little if any exchange had occurred. A typical kinetic experiment is outlined below. To hydrazone **2a** (25.4 mg) was added 0.2916 g of sulfolane and 0.2914 g of 5% $P_2O_5/MeSO_3H$. A time zero sample was taken and analyzed by HPLC, and then the septum-sealed flask was placed in a constant temperature bath at 40.0 °C. Weighed aliquots (20 mg) were removed via syringe and assayed via HPLC. Conditions for the HPLC were as follows: DuPont Zorbax 25 cm RX-C8 column; eluent consisting of 65% acetonitrile/35% 0.1% aqueous H_3PO_4; detection at 220 nm; flow of 1.5 mL per min; retention times: hydrazone **2a**, 3 min; indole **7a**, 7.5 min; indole **5a**, 8.5 min.

HPLC conditions for the other hydrazones and products were as follows. In all cases the column used was a DuPont Zorbax 25 cm RX-C8 column with a flow of 1.5 mL/min and detection at 220 nm. For conversion of hydrazone **1** to indole **4**, eluent was 50/50 acetonitrile/0.1% aqueous H_3PO_4; retention times were 2.0 min for **1** and 9 min for **4**. For conversion of hydrazone **3** to indoles **6** and **8**, eluent was 60/40 acetonitrile/0.1% aqueous H_3PO_4; retention times were 2.5 min for **3**, 9.6 min for **8**, and 10.1 min for **6**.

Reaction Products. 1,2-Dimethylindole (**4**) was obtained from Aldrich. Indoles **5–8** and **10** were isolated from indolization reactions and purified by silica gel chromatography followed by recrystallization. Characterization of indoles **5–8** was described before.[15] Characterization of indole **10** is given below.

Indole **10**: ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H, CH_3), 5.21 (s, 2 H, CH_2N), 5.45 (s, 2 H, CH_2O), 6.25 (s, 1 H, H-3 proton on indole), 6.88 (d, J = 8.5 Hz, 2 H, Cl-bearing ring), 6.9–7.2 (m, 3 H, aromatic), 7.23 (d, J = 8.5 Hz, 2 H, Cl-bearing ring), 7.51–7.58 (m, 1 H, aromatic), 7.71–7.84 (m, 3 H, aromatic), 8.10–8.19 (m, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 12.8 (q), 45.9 (q), 72.0 (t), 100.6 (d), 103.7 (d), 109.8 (d), 111.1 (d), 119.3 (d), 126.3 (d), 127.3 (d), 127.6 (s), 127.7 (d), 128.6 (s), 128.94 (degenerate d, two carbons), 129.7 (d), 132.5 (s), 133.1 (s), 136.4 (s), 136.9 (d), 137.3 (s), 147.6 (s), 153.0 (s), 158.9 (s). Anal. Calcd for $C_{26}H_{21}N_2ClO$: C, 75.63; H, 5.13; Cl, 8.59; N, 6.78. Found: C, 75.48; H, 5.01; Cl, 8.64; N, 6.69.

(14) House, H. O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362–3379.
(15) Zhao, D.; Hughes, D. L.; Bender, D. R.; DeMarco, A. M.; Reider, P. J. *J. Org. Chem.* **1991**, *56*, 3001–3006.

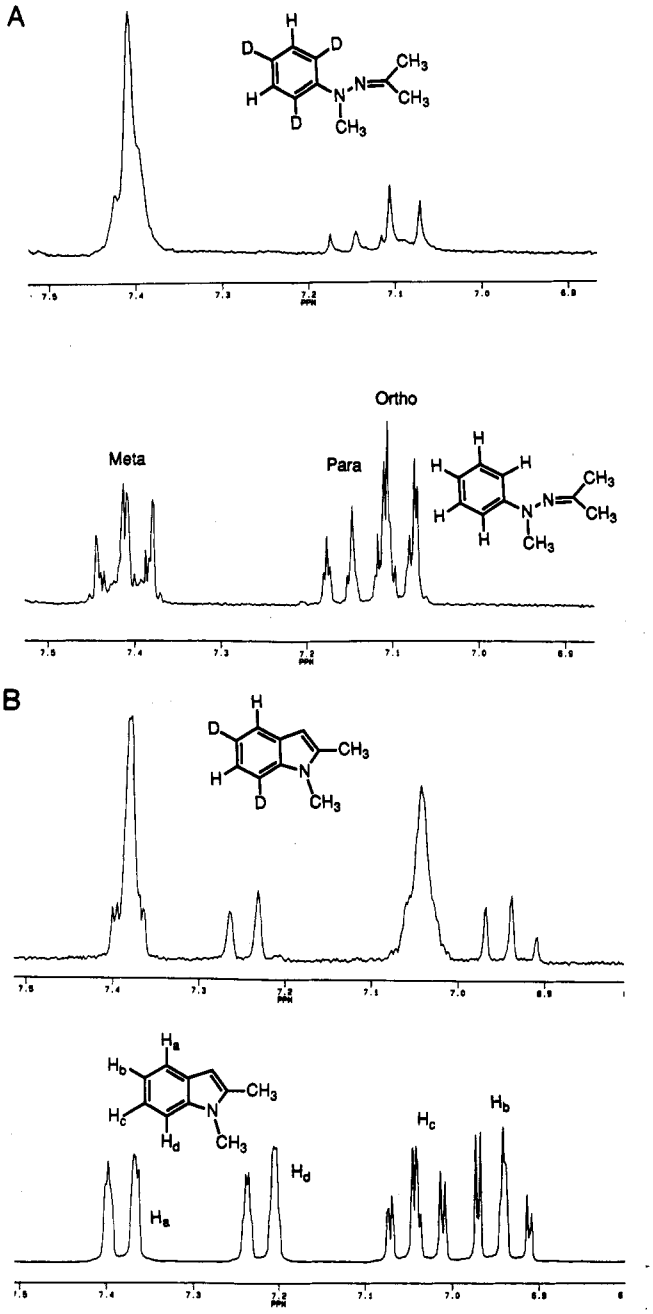


Figure 1. (A) ^1H NMR of aromatic region of ring-deuterated hydrazone **1a** (top) vs all protio hydrazone (bottom). (B) ^1H NMR of aromatic region of ring-deuterated indole **4a** (top) vs all protio indole (bottom).

^1H NMR Spectra of Hydrogen/Deuterium Exchange in the Aromatic Ring. The ^1H NMR of hydrazone **1a** is reproduced in Figure 1A. The ortho and para protons have exchanged about 80%, while the meta protons have not exchanged at all, based on integration compared to the NCH_3 group. Exchange of the ortho and para protons cause the meta protons to collapse into a singlet.

The ^1H NMR of indole **4a** is reproduced in Figure 1B. In this case, protons H_b and H_d are about 80% exchanged, while H_a and H_c are not exchanged. This results in collapse of H_b and H_d into singlets. H_b and H_d correspond to the para and ortho positions of the precursor hydrazone. The other ortho proton is lost during the tautomerization (Scheme I).