AN UNUSUAL PARABOLIC DEPENDENCE OF RATE ON ACIDITY IN THE FISCHER INDOLE REACTION

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Over the H_0 acidity range from $+2$ to -8, four different mechanistic variations occur in the Fischer indole reaction, leading to an unusual parabolic dependence of the rate constants on the acidity of the medium. In strongly acidic media kinetic isotope effects indicate that the rate-determining step is deprotonation to form the ene–hydrazine tautomer, whereas in weakly acidic media the tautomerization is so rapid that [3,3]-rearrangement becomes rate limiting. At an intermediate acidity, the deprotonation is rate determining, with the rate being strongly dependent on the concentration of the anionic counter ion.

INTRODUCTION

The Fischer indole reaction has found widespread use in organic synthesis over the past century and has also been the subject of numerous physical organic studies aimed at elucidating its mechanism.[1] The mechanism generally agreed upon is that proposed by Robinson and Robinson in 1924, as shown in Scheme 1 for the indolization of the N-methylphenylhydrazone of heptan-4-one (**1**).[2] Although the basic mechanism proposed 70 years ago has withstood the test of time, several aspects of the reaction have not been well defined or fully understood. Recently, based primarily on deuterium kinetic isotope effects, we demonstrated that the rate-determining step changed when the acidity of the medium was varied.[3] Under strong acid conditions, the tautomerization step (k_1 in Scheme 1) was

found to be rate determining, whereas under weak acid conditions, the [3,3]-rearrangement step (or possibly a later step) was shown to be rate determining. Since the acid is playing a key role in this reaction, we undertook a further study of the effect of the acid strength on rates, and found an unusual parabolic dependence, as described below.

EXPERIMENTAL AND RESULTS

Rate constants for the indolization of the N-methylphenylhydrazone of **1** were measured using HPLC[3] at 40 °C in varying mixtures of $MeSO_3H$ in sulfolane, in HOAc and in HOAc–sulfolane mixtures. The acidity of the medium (H_0 constants) was measured using the NMR technique of Fărcaşiu *et al.*[4] Table 1
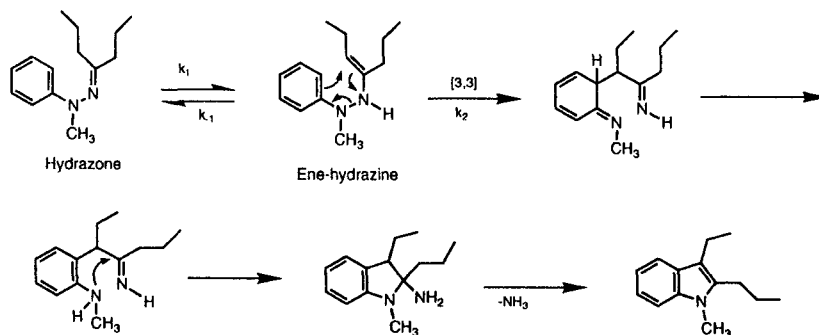
Scheme 1

Table 1. First-order rate constants at 40 °C for the indolisatiion of N-methylphenylhydrazone of Heptan-4-one (1) (0·03 M solution)

Entry	Acid/solvent	H_0	k (min^{-1})
1	Neat MeSO$_3$H	$-7·48^a$	$6·89 \times 10^{-3}$
2	7:3 MeSO$_3$H–sulfolane	$-6·73$	$1·97 \times 10^{-3}$
3	1:1 MeSO$_3$H–sulfolane	$-6·15$	$6·42 \times 10^{-4}$
4	1:2 MeSO$_3$H–sulfolane	$-5·17$	$2·37 \times 10^{-4}$
5	1:5 MeSO$_3$H–sulfolane	$-3·63$	$1·51 \times 10^{-4}$
6	1:10 MeSO$_3$H–sulfolane	$-2·37$	$4·78 \times 10^{-4}$
7	1:15 MeSO$_3$H–sulfolane	$-1·52$	$1·13 \times 10^{-3}$
8	1:25 MeSO$_3$H–sulfolane	$0·1$	$2·84 \times 10^{-3}$
9	1:45 MeSO$_3$H–sulfolane	$0·4^b$	$4·69 \times 10^{-3}$
10	MeCOOH	$(1)^c$	$1·82 \times 10^{-3}$
11	1:10 MeCOOH–Sulfolane	—	$8·3 \times 10^{-5}$

[a] Literature values include $-7·60^5$ and $-7·86.^6$
[b] Estimated value.
[c] Reported as 0 by Milyaeva[7] but considered anomalous by Rochester.[8] A value of 1 can be estimated based on H_0 of formic and chloroacetic acids.

lists the H_0 acidity constants and the first-order indolization rate constants measured at a hydrazone concentration of 0·03 M. Table 2 lists rate constants measured at differing hydrazone concentrations and with added salts, and also gives deuterium kinetic isotope effects for reactions in which both α-positions of the hydrazone have been exchanged with four deuterium atoms.

Effect of acidity on indolization rate constants

A Brønsted plot of log k vs. H_0 for the indolization of the hydrazone 1, shown in Figure 1, demonstrates that the rate constants have a parabolic dependence on the acidity of the medium. In the strong acid region from $H_0 = -7·5$ to -6, the points define a line with a slope of 0·77, indicating a strong dependence of rate on acidity in this reaction regime. In the region from $H_0 = -5$ to -2, there is a minimal dependence of rate on acidity with a change in slope, whereas in the -2 to $+1$ region there is an unusual and strong negative dependence on the acidity. In a more weakly acidic medium above $H_0 = +1$, such as solutions of acetic acid

Table 2. Effects of salts and hydrazone concentration on the first-order rate constants and kinetic isotope effects for the indolization of N-methylphenylhydrazone of heptan-4-one (1) in MeSO$_3$H-sulfolane solution at 40 °C

| Entry	Acid/solvent	H_0	Hydrogen isotope, concentration	Salt (concentration)	k (min^{-1})	k_H/k_D
1	Neat MeSO$_3$H	$-7·48$	H$_4$, 0·3 M	None	$5·62 \times 10^{-3}$	$5·4$
2	Neat MeSO$_3$H		D$_4$, 0·3 M	None	$1·03 \times 10^{-3}$	
3	Neat MeSO$_3$H		H$_4$, 0·03 M	None	$6·89 \times 10^{-3}$	
4	1:1 MeSO$_3$H–sulfolane	$-6·73$	H$_4$, 0·2 M	None	$4·60 \times 10^{-4}$	$4·2$
5	1:1 MeSO$_3$H–sulfolane		D$_4$, 0·2 M	None	$1·1 \times 10^{-4}$	
6	1:2 MeSO$_3$H–sulfolane	$-5·17$	H$_4$, 0·2 M	None	$1·96 \times 10^{-4}$	
7	1:5 MeSO$_3$H–sulfolane	$-3·63$	H$_4$, 0·2 M	None	$5·89 \times 10^{-4}$	
8	1:10 MeSO$_3$H–sulfolane	$-2·37$	H$_4$, 0·2 M	None	$7·43 \times 10^{-3}$	$2·6$
9	1:10 MeSO$_3$H–sulfolane		D$_4$, 0·2 M	None	$2·82 \times 10^{-3}$	
10	1:10 MeSO$_3$H–sulfolane		H$_4$, 0·01 M	None	$2·11 \times 10^{-4}$	$3·0$
11	1:10 MeSO$_3$H–sulfolane		D$_4$, 0·01 M	None	$7·08 \times 10^{-5}$	
12	1:10 MeSO$_3$H–sulfolane		H$_4$, 0·01 M	n-Bu$_4$NBF$_4$(0·20 M)	$2·61 \times 10^{-4}$	
13	1:10 MeSO$_3$H–sulfolane		H$_4$, 0·01 M	Et$_3$NH$^+$MeSO$_3^-$(0·21 M)	$2·50 \times 10^{-3}$	
14	1:10 MeSO$_3$H–sulfolane		H$_4$, 0·01 M	Et$_3$NH$^+$MeSO$_3^-$ (0·48 M)	$6·94 \times 10^{-3}$	
15	1:10 MeSO$_3$H–sulfolane		H$_4$, 0·01 M	Me$_4^+$N Cl$^-$(0·21 M)	$1·88 \times 10^{-2}$	$3·3$
16	1:10 MeSO$_3$H–sulfolane		D$_4$, 0·01 M	Me$_4^+$N Cl$^-$(0·21 M)	$5·66 \times 10^{-3}$	
17	1:15 MeSO$_3$H–sulfolane	$-1·52$	H$_4$, 0·03 M	None	$1·13 \times 10^{-3}$	$1·7$
18	1:15 MeSO$_3$D–sulfolane		D$_4$, 0·03 M	None	$6·49 \times 10^{-4}$	
19	1:15 MeSO$_3$H–sulfolane		H$_4$, 0·2 M	None	$7·39 \times 10^{-3}$	$1·5$
20	1:15 MeSO$_3$D–sulfolane		D$_4$, 0·2 M	None	$4·89 \times 10^{-3}$	
21	1:25 MeSO$_3$H–sulfolane	$0·1$	H$_4$, 0·03 M	None	$2·84 \times 10^{-3}$	$1·7$
22	1:25 MeSO$_3$D–sulfolane		D$_4$, 0·03 M	None	$1·62 \times 10^{-3}$	
23	1:25 MeSO$_3$H–sulfolane		H$_4$, 0·2 M	None	$7·72 \times 10^{-3}$	$1·1$
24	1:25 MeSO$_3$D–sulfolane		D$_4$, 0·2 M	None	$6·97 \times 10^{-3}$	
25	MeCOOH	1	H$_4$, 0·03 M	None	$1·82 \times 10^{-3}$	
26	MeCOOH		H$_4$, 0·3 M	None	$1·80 \times 10^{-3}$	$1·3$
27	MeCOOD		D$_4$, 0·3 M	None	$1·39 \times 10^{-3}$	
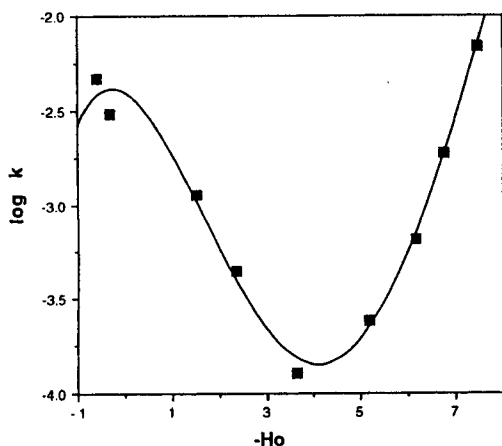
Figure 1. Brønsted plot of log k vs. $-H_0$ for the indolization of the N-methylphenylhydrazone of heptan-4-one (1) at 40 °C in MeSO$_3$H–sulfolane solution at a hydrazone concetration of 0.03 M

Figure 2. Plot of log k vs. log [MeSO$_3^-$] for the indolization of the N-methylphenylhydrazone of heptan-4-one (1) at 40 °C in 1 : 10 MeSO$_3$H–sulfolane solution

in sulfolane, the rate constants once again decrease sharply.

Concentration effects

During the course of measuring rates using 1 : 10 MeSO$_3$H–sulfolane, we noted that the rate constants increased when the hydrazone concentration was increased. We therefore initiated an investigation of the effects of hydrazone concentration and salts on the reaction rate. As shown in Tables 1 and 2, the rate constants are fairly insensitive to hydrazone concentration in the strongly acidic region of $H_0 = -7·5$ to -5 (compare entries 1 of Table 1 and 1 of Table 2, entries 3 of Table 1 and 4 of Table 2 and entries 4 of Table 1 and 6 of Table 2), are strongly sensitive in the $H_0 = -3$ to $-1·5$ region and are insensitive again in acetic acid as solvent. Since the hydrazones are protonated even in the weak acid media, as shown by ^{13}C NMR spectroscopy, this rate dependence is most likely a salt effect. Therefore, the reaction was carried out in the presence of various salts, as shown in Table 2. The data indicate that there is not a general salt effect, but rather a specific salt effect. Whereas the cation appears to be unimportant, the basicity of the anion plays a decisive role. With the non-basic anion tetrafluoroborate, only a small rate effect is observed. With the more basic anions MeSO$_3^-$ and Cl$^-$, which are the most basic anions this acidic medium can have owing to leveling effects, a strong rate dependence is observed. Figure 2 shows that a plot of log k vs. log[MeSO$_3^-$] (rate data from entry 6 of Table 1 and entries 10, 13 and 14 of Table 2) is linear with a slope of nearly unity, indicating that the reaction is essentially first order in salt concentration.
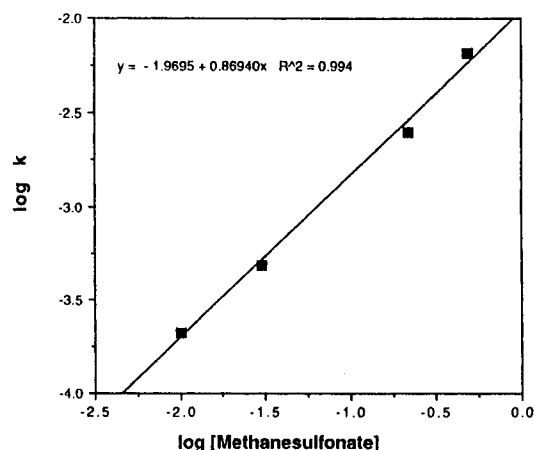
Deuterium kinetic isotope effects

As shown in Table 2, large kinetic isotope effects were measured for the indolization under the strong acid conditions, and decreased as the acidity of the medium decreased, such that at H_0 in the $-1·5$ to $+1$ range, k_H/k_D is near unity. This is the same effect observed earlier,[3] and indicates that at H_0 in the range -2 to $-7·5$ the initial tautomerization (k_1 in Scheme 1) is the rate-determining step. At an H_0 of -1 to $+1$, the lack of an isotope effect indicates that a later step, probably k_2 in Scheme 1, is now rate determining.

Summary of mechanistic changes

The parabolic dependence of the rate on acid strength (Figure 1) and the variable kinetic isotope effects (Table 2) indicate that a change in mechanism occurs as the acidity is varied. The data indicate that there are roughly four differing regimes.

(1) In the strong acidic medium, with H_0 between $-7·5$ and -5, the large isotope effect leaves no doubt that the rate-limiting step is the deprotonation in the initial tautomerization step (k_1). The probable tautomerization mechanism is shown in equation (1). The strong dependence on acid strength in this region indicates that the reactive species is the diprotonated hydrazone (with second protonation either on the ring or α- nitrogen), present in a small equilibrium quantity. (Diprotonation is also consistent with inverse solvent isotope effects in this H_0 region, as measured previously.[3]) The rate-determining deprotonation must involve a base, and since the reaction is insensitive to the concentration of the counter ion (MeSO$_3^-$), the basic source is probably the solvent or a hydrogen-

$$(1)$$

$$(2)$$
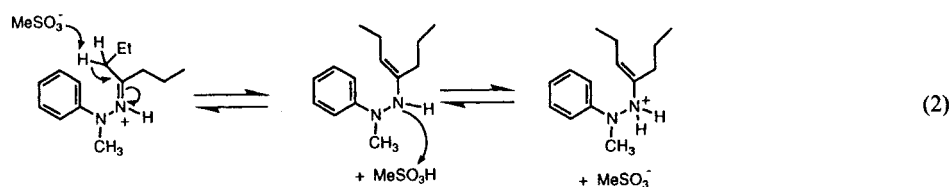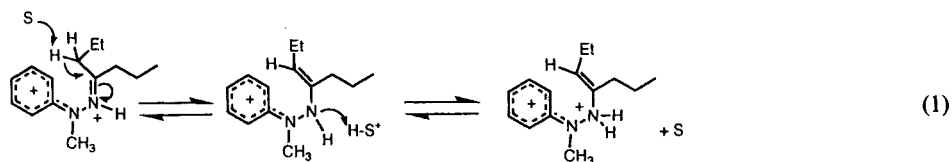
bonded conglomerate of $MeSO_3^-$ and $MeSO_3H$. Alternatively, a solvent-assisted intramolecular deprotonation may occur. This mechanism is similar to that postulated for acid-catalyzed ketone enolization, where protonation on the ketone oxygen occurs in a preequilibrium step followed by rate-determining deprotonation (for a comprehesive review of the kinetics and mechanism of enolization, see Ref. 9). In the enolization, the overall rates are strongly correlated with acidity, with rates increasing with increased acidity, again in analogy with the tautomerization under the strong acid conditions in the indolization reaction.

(2) In the H_0 region of -5 to -2, the k_H/k_D values are lower than in the more strongly acidic media, but the substantial values near 3 still indicate that the rate-limiting step is deprotonation. This region is characterized by a trough in the plot of log k vs acid strength, with a minimum near $H_0 = -4$ (Figure 1), and a nearly unit dependence on the concentration of the basic counter ion (Figure 2). This is consistent with a mechanistic change from diprotonation of the hydrazone to monoprotonation. This is shown in equation (2), where the base for deprotonation is the counter ion $MeSO_3^-$ or other added counter ion such as Cl^-.

(3) In the H_0 region of $-1\cdot5$ to $+1$ the isotope effects decrease to near unity, which indicates a mechanistic change in rate-determining step occurs in this region, from tautomerization at acidities stronger than $H_0 = 0 - 2$ to [3,3]-rearrangement at acidities weaker than $H_0 = 0$. The increase in rate in this region with decreasing acidity means that the initial tautomerization step is becoming increasingly more rapid as the acidity decreases, up to the point where it is no longer the ratedetermining step. In agreement with this, H–D exchange of the deuterated hydrazone 1 in DOAc was very rapid, with complete exchange occurring within 10 min at ambient temperature. In contrast, in CF_3COOH solution ($H_0 = -3\cdot0$), only 15% exchange occurs over a 45 h period at ambient temperature. This negative dependence on acidity is most unusual (this effect is common for several Fischer indole reactions

involving other hydrazones, and will be reported in due course) and can be interpreted perhaps as a decrease in hydrogen bonding to the $MeSO_3^-$ anion as the concentration of $MeSO_3H$ decreases, making it a more effective base, and hence accelerating the tautomerization rate. A similar effect has been seen previously in the Mitsunobu reaction, where reactions of formate ion were strongly influenced by the amount of hydrogen bonding to formic acid.[10]

(4) Above $H_0 = +1$, the reaction becomes very slow, as shown by rates in acetic acid–sulfolane mixtures. In this region, no protonation of the hydrazone occurs, as shown by ^{13}C NMR spectroscopy, indicating that monoprotonation accelerates the tautomerization step.

In summary, over the H_0 acidity range $+2$ to -8, four different mechanistic variations occur in the Fischer indole reaction, leading to an unusual parabolic dependence of the rate constants on the acidity of the medium.

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