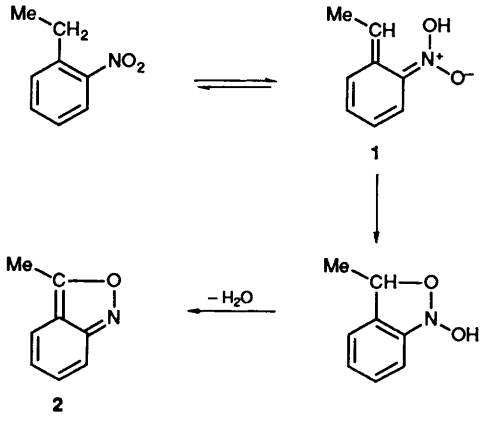
The Mechanism of Cyclisation of 1-Ethyl-2-nitrobenzene to give 3-Methylanthranil in Trifluoromethanesulfonic acid. Evidence for an Intramolecular Hydrogen Transfer

Rupert P. Austin and John H. Ridd *
Chemistry Department, University College, 20 Gordon Street, London UK WC1H 0AJ

Deuterium labelling has been used to show that the cyclisation in trifluoromethanesulfonic acid of 1-ethyl-2-nitrobenzene to 3-methylanthranil does not proceed through an equilibrium concentration of the *aci*-form of the substrate. Instead, the rate-determining step appears to involve the intramolecular transfer of hydrogen from the α-carbon atom to one of the oxygen atoms of the protonated nitro group. This conclusion is supported by semi-empirical molecular orbital calculations.

1-Ethyl-2-nitrobenzene has recently been shown[1] to undergo dehydration and cyclisation to form 3-methylanthranil **2** (Scheme 1) in trifluoromethanesulfonic acid at 90 °C; no other products were detected and, from the NMR spectra, the yield appeared to be quantitative. The product was shown to be identical to a sample of 3-methylanthranil prepared by a standard method. The reaction was considered to occur through an equilibrium concentration of the *aci*-form of 1-ethyl-2-nitrobenzene **1**, as shown in Scheme 1. This mechanism



Scheme 1

accords with that suggested for the general acid-catalysed formation of anthranils from 2-nitrobenzyl systems.[2,3] However, recent evidence[4] that protonated nitro groups act as hydride ion acceptors in trifluoromethanesulfonic acid has led us to reconsider this mechanism and the studies now reported show it to be incorrect.

Results

The rate of cyclisation of 1-ethyl-2-nitrobenzene was followed from the change in the height of the central component of the methyl triplet in the ^{1}H NMR spectrum of the starting material. Good first-order kinetics were observed during an individual run although there was evidence for a slight decrease in the first-order rate coefficient when the concentration of the substrate was increased. The resulting first-order rate coefficients are given as a function of acidity in Table 1 and plotted against the H_0 function in Fig. 1, curve (*a*). These H_0 values are calculated from the extent of protonation of picramide and *p*-nitrotoluene in trifluoromethanesulfonic acid[5] at 25 °C but are based on the assumption that the pK_a of picramide[6] is −10.0 since the full

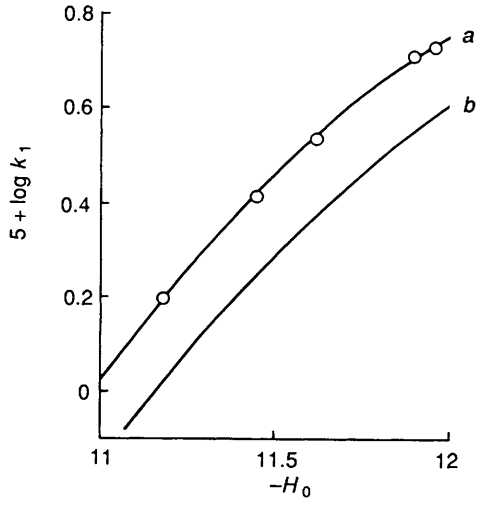


Fig. 1 Curve (*a*); the variation of log k_1 with H_0 for the conversion of 1-ethyl-2-nitrobenzene to 3-methylanthranil in aqueous trifluoromethanesulfonic acid. Curve (*b*); the curvature expected in a unimolecular reaction occurring in the conjugate acid of a hypothetical substrate with pK_a = −12.

acidity function for trifluoromethanesulfonic acid is not yet available. This acidity dependence was missed in the preliminary kinetic study[1] probably because the temperature of one of the two kinetic runs was incorrectly recorded.

1-(1-^{2}H$_2$)Ethyl-2-nitrobenzene has been prepared by the reduction of acetophenone with lithium aluminium deuteride followed by nitration and the separation of the isomers by preparative GLC. The extent of reaction of this compound in trifluoromethanesulfonic acid has been followed from the decrease in the height of the methyl singlet in the ^{1}H NMR spectra. During reaction, this peak remains a singlet and there is no formation of the quartet derived from the $-CH_2-$ group in the undeuteriated substrate (Fig. 2); it appears therefore that cyclisation occurs without any exchange of the $-CD_2-$ deuterons with the medium. The rate of reaction of the deuteriated substrate is significantly slower than the normal substrate (Table 1), giving an isotope effect of k_H/k_D = 3.1 at 100 °C.

Studies have also been carried out on the reactions of 1-methyl-2-nitrobenzene in 98.9% trifluoromethanesulfonic acid at 100 °C. The overall reaction is extremely slow but, after 14 days, the height of the methyl singlet relative to 1,4-dinitrobenzene (present as an NMR standard) is reduced by a factor of two. However, the comparison of the aromatic region

Table 1 First-order rate coefficients (k_1) for the cyclisation of 1-ethyl-2-nitrobenzene and 1-(1-$^2H_2$)ethyl-2-nitrobenzene in aqueous trifluoromethanesulfonic acid at 100 °C (except where indicated). Tetramethylammonium trifluoromethanesulfonate (TMAT) was used as the standard for integration except where indicated

Substrate (S)	[S]/mol dm^{-3}	Acid(%)	$-H_0$	[TMAT]/mol dm^{-3}	10^5k_1/s^{-1}
$CH_3CH_2C_6H_4NO_2$	0.11	96.5	11.18	0.018	1.57
$CH_3CH_2C_6H_4NO_2$	0.11	97.46	11.45	0.018	2.60
$CH_3CH_2C_6H_4NO_2$	0.11	97.98	11.62	0.018	3.46
$CH_3CH_2C_6H_4NO_2$	0.11	98.68	11.90	0.018	5.15
$CH_3CH_2C_6H_4NO_2$	0.11	98.87	11.96	0.018	5.38
$CH_3CH_2C_6H_4NO_2$	0.409	99.06	12.04	0.045[a]	3.31[b]
$CH_3CH_2C_6H_4NO_2$	0.409	99.06	12.04	0.045	3.30[b]
$CH_3CH_2C_6H_4NO_2$	0.369	98.86	11.95	0.122[c]	3.93
$CH_3CD_2C_6H_4NO_2$	0.369	98.86	11.95	0.122[c]	1.31

[a] In the presence of *p*-dinitrobenzene (0.122 mol dm^{-3}). [b] At 96.3 °C. [c] With *p*-dinitrobenzene replacing tetramethylammonium trifluoromethanesulfonate as the NMR standard.

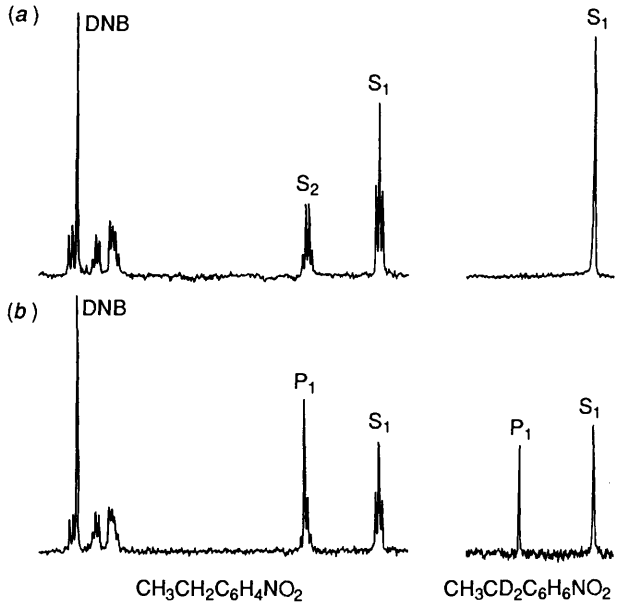


Fig. 2 ^{1}H NMR spectra taken during the cyclisation reactions of 1-ethyl-2-nitrobenzene and 1-(1-$^2H_2$)ethyl-2-nitrobenzene in 98.86% trifluoromethanesulfonic acid at 100 °C (a) at the start of reaction and (b) after *ca.* 40% reaction. For the deuterated compound, only the aliphatic region of the spectrum is shown since the aromatic regions of the two spectra are identical. S_1, Methyl signal of starting material; S_2, methylene signal of starting material, P_1, methyl signal of product. For chemical shifts, see ref. 1 and Experimental section.

with that of synthetic mixtures indicates that less than 50% of anthranil has then been formed. Anthranil is stable under these conditions and so the comparison of this result with the rate coefficients in Table 1 indicates that the rate of cyclisation of 1-methyl-2-nitrobenzene is less than that of the corresponding ethyl compound by a factor that is at least 70 and probably considerably larger.

Discussion

The results reported above immediately rule out reaction through an equilibrium concentration of the *aci*-form **1** since this would lead to H/D exchange in the methylene group during reaction. If the *aci*-form is involved in the reaction, it must therefore be formed in the rate-determining step. The kinetic isotope effect observed (Table 1) (equivalent to $k_H/k_D = 4.1$ at 25 °C) indicates a rate-determining fission of one of the methylene C–H bonds. This would normally be understood as a rate-determining proton loss to the solvent or to some base in the medium.

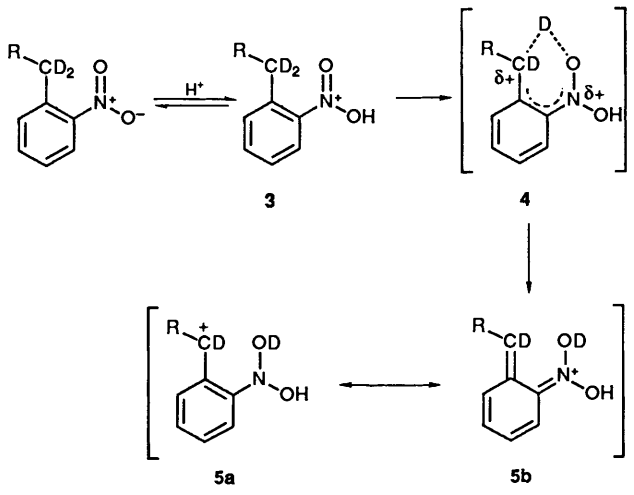
There are however considerable difficulties with this interpretation. One comes from the fact that this reaction shows strong acid catalysis [Fig. 1, curve (*a*)]. The expected curvature of a plot for reaction through a protonated substrate with a pK_a of −12 is also shown [Fig. 1, curve (*b*)]. The pK_a of 1-ethyl-2-nitrobenzene does not appear to have been measured but the pK_a of 1-methyl-3-nitrobenzene has been given [7] as −11.99. The similarity in the curvature of the theoretical and experimental curves is obvious and greater than might have been expected in view of the temperature difference (the H_0 values refer to 25 °C). The results therefore point strongly to reaction through the monoprotonated substrate. However, the general acid catalysed conversion of nitro compounds to the *aci*-forms has been sought but not found; the present position has been summarised by Lewis.[8] We have also investigated whether there is any general acid catalysed formation of *aci*-nitrocompounds in trifluoromethanesulfonic acid by determining whether any H/D exchange occurs with deuterated nitromethane in this medium. No exchange could be detected by ^{1}H NMR spectroscopy, even after several hours at 70 °C, but some decomposition occurred.

Another difficulty with the above interpretation comes from a comparison of the substituent effects involved. In the base catalysed formation of the *aci*-form of nitrocompounds by proton loss from the α-carbon atom, methyl substitution at the α-position markedly slows down the rate of reaction (nitromethane, 1; nitroethane, 0.164; nitroisopropane, 0.0087).[9] In contrast, the relative rates of reaction of 1-methyl-2-nitrobenzene and 1-ethyl-2-nitrobenzene in this cyclisation reaction indicate that such methyl substitution increases the reaction rate by a factor of > 70. This large rate factor suggests that a partial positive charge is created at the reacting carbon atom in the transition state.

We have therefore to consider a rate-determining step involving the effective loss of a hydride ion from the methylene group. From our related studies on the oxidising power of nitro compounds in trifluoromethanesulfonic acid,[4] one possible recipient of the hydride ion would be the *p*-dinitrobenzene present as an NMR standard in a few of the runs.* However, the *p*-dinitrobenzene does not become involved, for the rate of formation of the anthranil is unchanged when *p*-dinitrobenzene is present (compare the results for runs 6 and 7 in Table 1).

Trifluoromethanesulfonic acid is not itself a strong oxidising agent[10] and so we suggest that the rate-determining step involves the intramolecular transfer of the hydrogen from the methylene group to an oxygen atom of the protonated nitro group (Scheme 2). Such a reaction can be described in two ways, depending on how the structure of the product **5**(R = Me) is

* These runs were carried out before we became aware of the possible involvement of *p*-dinitrobenzene in hydride transfer reactions.



Scheme 2

Table 2 Calculated standard heats of formation of the initial states (IS), transition states (TS), and final states (FS) for the intramolecular hydrogen transfers illustrated in Schemes 2 and 3. The reacting species are protonated 1-ethyl-2-nitrobenzene (A), protonated 1-methyl-2-nitrobenzene (B), and unprotonated 1-ethyl-2-nitrobenzene (C); the structures involved are indicated in parentheses. The final column indicates the difference between the heats of formation of the transition state and the initial state. The calculations were carried out by the AM1 method and refer to the unlabelled compounds

Reacting species	H_f°/kJ mol^{-1}			ΔH_f°/kJ mol^{-1}
	IS	TS	FS	
A	786.2(3)	945.5(4)	756.2(5)	159.3
B	809.7(3)	994.6(4)	818.1(5)	184.9
C	58.3(6)	275.1(7)	176.9(8)	216.8

Table 3 Calculated charge distributions for the initial state, transition state, and final state in the hydrogen transfer reaction involving protonated 1-ethyl-2-nitrobenzene. The calculations were carried out by the AM1 method and refer to the unlabelled compounds

Species	Charges		
	Alkyl group[a]	Ring (C_6H_4)	Nitro group[b]
Initial state (**3**)	0.174	0.368	0.458
Transition state (**4**)	0.477	0.362	0.161
Final state (**5**)	0.576	0.350	0.074

[a] Taken as $-C_2H_5$ in structures **3** and **4**, and as $-C_2H_4$ in structure **5**. [b] Taken as $-NO_2H$ in structures **3** and **4**, and as $-NO_2H_2$ in structure **5**.

written. If structure **5a** were considered to represent the resulting compound, the reaction becomes equivalent to a hydride transfer but, if the product were written as structure **5b**, the reaction becomes formally equivalent to a [1,5]sigmatropic shift. The substituent effect of the methyl group requires therefore that the product **5** resembles structure **5a**. The subsequent reactions of species **5**(R = Me), following proton loss to the medium, could then be as described in Scheme 1.

To check whether this mechanism is reasonable, semi-empirical molecular orbital calculations have been carried out on this hydrogen transfer in protonated 1-ethyl-2-nitrobenzene **3**(R = Me), protonated 1-methyl-2-nitrobenzene **3**(R = H), and unprotonated 1-ethyl-2-nitrobenzene **6** (Scheme 3); the calculations refer to the undeuterated compounds and, for each substrate, include the initial state, the transition state, and the product resulting from the proton transfer. The relevant heats of formation are given in Table 2, the changes in the charge

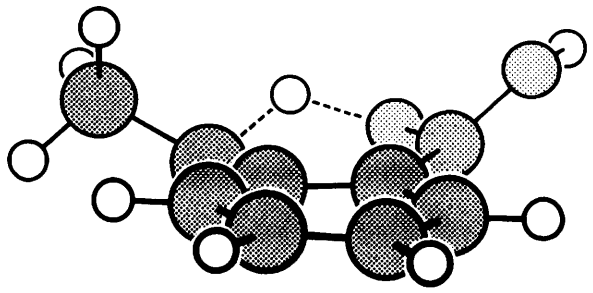
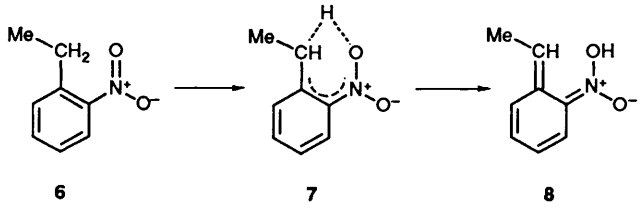


Fig. 3 The geometry of the calculated transition state (AM1 method) for the intramolecular hydrogen transfer in the reaction of the conjugate acid of 1-ethyl-2-nitrobenzene

distribution for the reaction of protonated 1-ethyl-2-nitrobenzene are shown in Table 3 and, for this substrate, the form of the transition state is shown in Fig. 3.

The calculated geometry of the transition state (with the migrating hydrogen above the plane of the benzene ring) would be consistent with a [1,5]sigmatropic shift but the charges in Table 3 indicate that moving from the initial state to the transition state results in the transfer of a charge of *ca.* 0.3 e from the alkyl group to the nitro group; a larger transfer of *ca.* 0.4 e occurs in the overall reaction. This is consistent with the large substituent effect of the methyl group and accords with the much greater value of ΔH_f° observed for the rearrangement in Scheme 2 when R = H compared with that when R = Me (Table 2). A similar calculation of ΔH_f° for the corresponding proton transfer in the unprotonated substrate (Table 2, Scheme 3) supports the view that protonation of nitro group favours the hydrogen transfer reaction.*



Scheme 3

The calculated characteristics of this reaction path are hence in agreement with the features observed. We consider therefore that this reaction can be regarded to some extent as the intramolecular equivalent of the intermolecular hydride transfer reactions reported previously for this solvent.[4] The fact that the geometry of the transition state is appropriate for an allowed [1,5]sigmatropic shift probably explains why this type of hydrogen transfer occurs with 1-ethyl-2-nitrobenzene and not with nitromethane (for the latter would involve a forbidden [1,3]sigmatropic shift). The calculations for the unprotonated substrate (Table 2) suggest that a similar hydrogen transfer should occur in that molecule by a slower thermal reaction. It may be significant therefore that 2-nitrodiarylmethanes form 3-arylanthranils on heating in paraffin oil to 300 °C.[11] A related direct transfer of hydrogen to the nitro group is also seen in the cation radicals of 1-alkyl-2-nitrobenzenes for it is the first step in the loss of an hydroxyl radical from these substrates in the mass spectrometer.[12]

Experimental

Materials.—1-Ethyl-2-nitrobenzene, 1-methyl-2-nitrobenz-

* The enthalpy changes have not been designated as enthalpies of activation since the corresponding changes in zero-point energy have not been included. The actual values will be changed by solvation; it is the relative values that are significant here.

ene, [$^2H_3$]nitromethane, acetophenone, and lithium aluminium deuteride were bought from Aldrich. Acetophenone (6.1 g) in diethyl ether (10 cm^3) was slowly added to a mixture of anhydrous aluminium chloride (12 g) and lithium aluminium deuteride (2 g) in diethyl ether (40 cm^3) at a rate that kept the mixture refluxing. After 30 min, dilute hydrochloric acid (2 mol dm^{-3}, 20 cm^3) was added and the mixture was extracted with diethyl ether (3 × 25 cm^3). Drying over $CaCl_2$ and removal of the solvent gave crude 1-[1-$^2H_2$]ethylbenzene (3.95 g). This was slowly added to a mixture of concentrated nitric acid (3 cm^3) and concentrated sulfuric acid (3 cm^3) maintained below 30 °C. After complete addition, the mixture was heated to 50 °C for 1 h and then added to water (40 cm^3). After extraction with diethyl ether, the mixture of isomers was separated by preparative GLC using a 10 ft × 3/8 in column packed with C20M on Chromosorb W and temperature programming (150–230 °C, 2 °C min^{-1}).

Kinetics.—A solution of the substrate and the standard (*p*-dinitrobenzene or tetramethylammonium trifluoromethanesulfonate) in trifluoromethanesulfonic acid of the required concentration was placed in an NMR tube and the ^1H NMR spectrum taken using a 100 MHz JEOL CW or a Varian 400 MHz FT spectrometer. The tube was then transferred to an oil bath at 100 °C and, after 30 s, the stopwatch was started. At appropriate intervals (30–120 min depending on the reaction rate), the tube was removed from the oil bath, brought rapidly to room temperature using a water bath, and the ^1H NMR spectrum of the solution taken as before. The tube was then replaced in the oil bath with 30 s being allowed as the warming up period. The height of the methyl signal in the substrate (δ 1.31, based on δ 3.1 for the tetramethylammonium ion [13]) was measured relative to that of the standard, and the amount of the substrate remaining was calculated from the corrected height of this methyl signal at time t divided by that at $t = 0$. The reactions were followed for up to 10 h. The first 7 kinetic runs in Table 1 (followed using the 400 MHz Varian spectrometer) gave excellent first-order kinetics but the others (followed using the 100 MHz JEOL spectrometer) gave some scatter with standard errors in the rate coefficients of *ca.* 10%.

The theoretical plot [Fig. 1, curve (*b*)] is that of $\log[c_{BH^+}/(c_{BH^+} + c_B)]$ calculated from the listed H_0 values for a substrate with $pK_a = 12$. The position on the vertical axis is arbitrary.

Molecular Orbital Calculations.—Initial estimates of the geometry of the structures **3** and **5** were obtained by a molecular mechanics program (PCMODEL-PI) [14] followed by full optimisation using the semi-empirical AM1 method in the MOPAC 6.0 program [15] implemented on a 486 PC. The structure of the transition state **4** was obtained from MOPAC 6.0 using the optimised geometries of structures **3** and **5** and the procedure of Dewar, Healy and Stewart [16] (Keyword SADDLE). The transition state geometry so obtained was further optimised using the eigenvector following method (Keyword TS), and the resulting transition state structures had the expected single negative eigenvalue in the Hessian matrix. The calculations were repeated using the PM3 method; this gave a similar pattern of relative energies and charge distributions leading to the same conclusions.

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