^{1}H NMR Studies of Proton Transfer and σ-Complex Formation in the Reactions of *N*-Substituted Picramides with Oxygen and Nitrogen Bases

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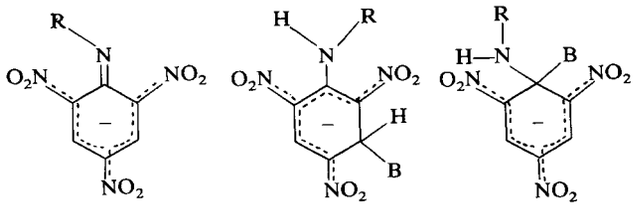
^{1}H NMR measurements of *N*-substituted picramides in dimethyl sulphoxide-methanol containing sodium methoxide show that the two major modes of 1:1 interaction involve transfer of an amino proton to give the conjugate base or methoxide attack at the 3-position to give a σ-adduct. The proportion of parent reacting by the latter pathway increases as the proportion of methanol in the solvent increases. Some comparative measurements in isopropanol-dimethyl sulphoxide show that relative to methoxide the isopropoxide ion has a greater propensity for proton abstraction than for base addition. Reaction of the substrates with amide ions derived from piperidine or from benzylamine gives σ-complexes by attack at unsubstituted ring positions. In the benzylamide adducts spin coupling is observed between the amino proton and the adjacent ring and methylene protons.

Proton magnetic resonance spectroscopy has proved useful in determining the structures of the adducts formed from aromatic nitro compounds and bases.[1] The likely modes of 1:1 interaction of picramide (2,4,6-trinitroaniline) and its *N*-substituted derivatives with bases (B^-) involve transfer of an amino proton to give the conjugate base **1**, or base addition at the 3-position to give the σ-complex **2**, or at the 1-position to give **3**. Measurements[2,3] on solutions of picramide, *N*-methylpicramide and *N,N*-dimethylpicramide in dimethyl sulphoxide (DMSO) containing methanolic sodium methoxide have been interpreted in terms of structures **1** and **2**. Thus, in the case of *N*-methylpicramide spin-coupled bands at δ 6.16 and 8.48 were attributed to the 3-methoxy adduct **2** (R = Me, B = OMe), while the upfield shift of the remaining ring proton resonance with increasing base concentration was attributed to proton loss from the amino group. Magnetic non-equivalence of the ring protons of **1** (R = Me) in solutions containing a slight excess of base was attributed to slow rotation about the ring carbon–nitrogen bond. Examples of addition at the 1-position to give complexes of type **3** have been found in the reactions of picryl ethers with aliphatic amines[4,5] and in the reaction of 2,4,6-trinitroanilino-*N*-methylpropionamide with methoxide ions[6] (gives **3**, R = CHMeCONHMe, B = OMe). In a recent paper Grudtsyn and Gitis[7] reported that in basic solution hydroxylamine adds at the 1-position to give complexes of type **3** (R = Me, B = NHOH), and also suggested that the major interaction of *N*-methylpicramide with methoxide ions gave **3** (R = Me, B = MeO).



1 **2** **3**

In this paper we examine the ^{1}H spectra produced from picramide and several of its derivatives in reaction with methoxide ions or isopropoxide ions and show that the major products are of type **1** and **2**. We also show that the anions derived from piperidine and benzylamine add at the 3-position of the substrates to give complexes of type **2**.

RESULTS AND DISCUSSION

Oxygen bases

The effects of varying the base concentration on the ^{1}H NMR spectra of picramide and its derivatives (0.2 M) were examined. Most measurements refer to a solvent system of 87/13 (v/v) DMSO-methanol although for comparison some measurements were made in 50/50 mixtures. In some cases the effects of potassium isopropoxide in 83/17 (v/v) DMSO-isopropanol were also investigated.

The results are best interpreted by Scheme 1 which will be justified later.

In the case of picramide, increasing the proportion of sodium methoxide results, as shown in Table 1, in a shift to high field in the ring proton resonance which remains sharp, and in the appearance of spin-coupled bands at δ 6.15 and 8.60. The latter bands are attributed to the adduct **2** (R = H, B = OMe), the high-field shift of one band being consistent with the covalency change at this position. The results indicate that on the

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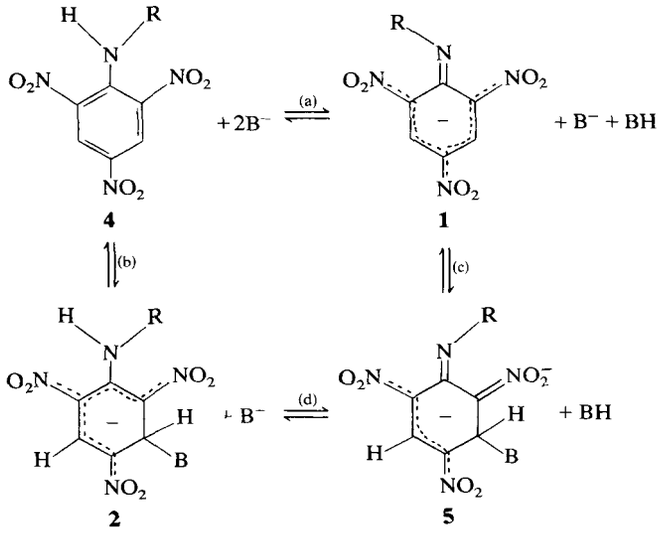


Scheme 1. Modes of 1:1 and 1:2 interaction of picramide and its derivatives with base.

NMR time scale equilibrium (a) is rapid, equilibrium (b) is slow, and both the intensities and shifts indicate that 35% of the 1:1 interaction results in proton loss. As the mole ratio of methoxide:picramide is increased from 1:1 to 2:1 the spin-coupled bands show a gradual change in position, consistent with the formation of **5** (R = H, B = OMe) with equilibrium (d) rapid.

The spectra obtained with potassium isopropoxide indicate that 1:1 interaction results largely (>90%) in proton transfer and in a solution of mole ratio 1:1.06 separate bands are observed for the ring protons of **1** (R = H).

Spectra obtained from *N*-methylpicramide and sodium methoxide were as found previously[2,3] and are interpreted in terms of Scheme 1 with equilibria (a) and (d) rapid and (b) and (c) slow. The major 1:1 interaction in the presence of potassium isopropoxide is proton loss to give **1** (R = Me). In the presence of more than 1 equivalent of base the spectrum shows spin-coupled bands $J = 3$ Hz at δ 8.22 and 8.16 due to restricted rotation about the C=NR bond.

In 83/17 DMSO-methanol the major ionization of *N*-isopropylpicramide is proton loss. Thus, increase in base concentration causes the ring proton resonance to

Table 1. Chemical shift data for reaction of picramide with sodium methoxide in 87/13 DMSO-methanol

Ratio [NaOMe]/[Picramide]	δ Ring	δ Ring (calc.)[a]	δ Adduct
0	9.07		
0.12	9.03	9.04	6.15, 8.60
0.23	9.03	9.01	6.15, 8.60
0.59	8.82	8.85	6.15, 8.60
0.94	8.46	8.53	6.15, 8.60
1.05	8.43	8.43	6.15, 8.60
1.29			6.20, 8.66
1.52			6.21, 8.71
1.87			6.24, 8.76
2.34			6.26, 8.77
2.93			6.25, 8.77

[a] Calculated assuming 35% ionization by proton loss.

Table 2. Chemical shifts of parent molecules in DMSO

Substituent[a]	Ring protons	Alkyl	Amino
NH_2	9.07	—	9.0
NHMe	8.92	2.82	9.25
$NHPr^i$	8.96	1.28(d), 3.4 (m)	8.6
$NHBu^t$	8.96	1.33	7.9
NMe_2	8.84	2.89	—

[a] Parent molecules are regarded as 1-substituted-2,4,6-trinitrobenzenes.

move to high field and with greater than 1 equivalent of base spin-coupled bands ($J = 3$ Hz) are observed due to slow rotation in the conjugate base **1** (R = isopropyl). However, in a 50/50 solvent system methoxide attack competes with proton transfer and anions of types **1** and **2** are formed in equal concentration. The spectra of the adducts **2** and **5** (R = isopropyl, B = OMe) show non-equivalence of the methyl groups in the isopropyl substituent.

As the ratio of sodium methoxide to *N*-*tert*-butylpicramide is increased in 90/10 DMSO-methanol new bands increase in intensity at the expense of the parent bands. Singlets at δ 8.20 and 1.15 are attributed to the conjugate base **1** (R = *tert*-butyl), while the 3-methoxy adduct **2** (R = *tert*-butyl, B = OMe) shows bands at δ 10.65 (NH), 8.45 and 6.20 (ring protons) and 1.40 (butyl). In this case both equilibria (a) and (b) are slow so that separate bands are observed due to amino protons and to hydroxylic protons in the solvent. A further interesting feature is that in the presence of excess base the ring proton resonance of the conjugate base **1** (R = *tert*-butyl) remains sharp, indicating rapid rotation about the ring-carbon to nitrogen bond. In a 50/50 solvent rapid exchange is observed between the parent and the anion formed by proton loss.

Chemical shift data are summarized in Tables 2–5.

Mode of ionization

Our results show that one mode of 1:1 interaction involves base attack at the 3-position. Thus, the proton at the 3-position shows a large shift to high field, consistent with a change in hybridization at this ring position. For *N*,*N*-dimethylpicramide this is the only 1:1 interaction observed. The second interaction has been ascribed in Scheme 1 to proton transfer to give the conjugate base **1**, but we must consider the possibility[7] that this interaction gives the 1-alkoxy adducts

Table 3. Chemical shifts of conjugate bases 1 in DMSO containing 10–20% alcohol

R, Structure 1	Ring protons	Alkyl substituent
H[a]	8.43	—
H[b]	8.05, 8.70	—
Me[a]	8.22(d), 8.60(d)	2.81
Me[b]	8.22(d), 8.61(d)	—
Isopropyl[a]	8.18(d), 8.53(d)	1.03(d)
tert-But[a]	8.20	1.15

[a] Base is methoxide in methanol.
[b] Base is isopropoxide in isopropanol.

Table 4. Chemical shifts of alkoxide adducts 2 in DMSO containing alcohol

Structure 2		Ring protons[a]	Alkyl substituent
R	B		
H	OMe	6.15, 8.60	
Me	OMe	6.16, 8.50	
Isopropyl	OMe	6.23, 8.55	1.16(d), 1.39(d)
tert-But	OMe	6.20, 8.45	1.40, 10.65(NH)
NMe_2[b]	OMe	6.20, 8.50	2.84
NMe_2[b]	OPr^i	6.30, 8.50	

[a] All bands are doublets $J \sim 1.5$ Hz.
[b] Adducts of *N,N*-dimethylpicramide.

Table 5. Chemical shifts of di-anions 5 in DMSO containing alcohol

Structure 5		Ring protons[a]	Alkyl substituents
R	B		
H	OMe	6.25, 8.77	—
H	OPr^i	6.45, 8.75	—
Me	OMe	6.15, 8.65	—
Me	OPr^i	6.30, 8.65	—
Isopropyl	OMe	6.10, 8.63	1.24(d), 0.98(d)
tert-But	OMe	6.00, 8.40	1.30

[a] All bands are doublets, $J \sim 1.5$ Hz.

of type **3**. Because the solvent contains alcohol NMR observation of bands due to added alkoxy groups is not possible. All the evidence favours proton transfer. Thus, in the case of *N*-methylpicramide identical spectra are observed using methoxide or isopropoxide ions as base. This is quite consistent with proton transfer to give **1** (R = Me), but would not be expected if different species **3** (R = Me, B = OMe) and **3** (R = Me, B = OPr^i) were formed. Secondly, the *N*-alkyl substituents show relatively small changes in chemical shift on reaction with base. If alkoxide attack had occurred at the 1-position then larger changes of chemical shift would be expected. For comparison, methoxide addition at the 1-position of 2,4,6-trinitroanisole results in a shift to high field of 1 ppm in the methoxyl resonance.[2,3] The third argument in favour of proton transfer lies in the rapid interconversion of parent and anion in solutions where both are present. Thus, in general, time-averaged bands are observed for the ring protons of parent and anions **1**. This is quite consistent with proton transfer to and from nitrogen, which in hydroxylic solvents is likely to be fast, but is not compatible with carbon–oxygen bond formation which is a slow process on the NMR time scale.[8] Nevertheless, we find that in 90/10 DMSO-methanol containing sodium methoxide interconversion of **4** and **1** (R = *tert*-but) is slow, and that bands are observed due to the amino protons in **4** and in **2** (R = *tert*-but, B = OMe). This may be ascribed to the size of the tertiary butyl group which will inhibit solvation of the amino group. Since proton transfer will almost certainly require initial hydrogen bond formation to methanol in the solvent, shielding of the amino proton from the solvent will result in a reduced rate of proton transfer.

The NMR spectra are in accord with 1:2 interaction giving species **5** resulting from base addition and proton loss. In media rich in DMSO used in the present work we have not observed 1:3 interaction. However, visible spectral measurements in concentrated sodium methoxide solutions give evidence for 1:3 interaction which probably results from proton transfer plus base addition at the 3- and 5- ring positions. The formation of multi-charged adducts is more likely in methanol, a solvent able to solvate localized negative charges, than in DMSO.

Solvent effects

The relative proportions of proton transfer and 3-alkoxy addition occurring in 1:1 interaction are given in Table 6. The data show that increasing the proportion of methanol in the solvent favours base addition relative to proton loss. This is expected since, as shown in Eqn (1), the two types of complex differ by one molecule of methanol.

Table 6. Mode of 1:1 ionization of *N*-substituted picramides

Substituent[a]	Base	Solvent	Ratio 1:2
NH_2	Methoxide	87/13 DMSO-methanol	35:65
NH_2	Isopropoxide	83/17 DMSO-isopropanol	<90:10
NHMe	Methoxide	87/13 DMSO-methanol	90:10
NHMe	Isopropoxide	83/17 DMSO-isopropanol	>90:10
$NHPr^i$	Methoxide	87/13 DMSO-methanol	>90:10
$NHPr^t$	Methoxide	50/50 DMSO-methanol	45:55
$NHBu^t$	Methoxide	90/10 DMSO-methanol	70:30
$NHBu^t$	Methoxide	50/50 DMSO-methanol	25:75

[a] Parents are regarded as substituted-2,4,6-trinitrobenzenes.

$$PicNR^- + MeOH \rightleftharpoons PicNHR{\cdot}OMe^- \quad (1)$$

The data also indicate that isopropoxide ions show, relative to methoxide, a greater propensity for proton transfer than for base addition.

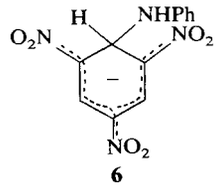
Rotation in conjugate base

When exchange with the parent molecules is slow the spectra of the anions **1**, (R = H, Me, isopropyl) show non-equivalence of the ring protons. This derives from slow rotation about the ring carbon to *N*-alkyl bond. That no such non-equivalence is observed in the spectrum of the anion **1** (R = *tert*-but) indicates that rotation is more rapid here and reflects the greater steric strain associated with the conformation in which the tertiary butyl group is in the ring plane. These results are in accord with those of von Jouanne and Heidberg[9] who measured the temperature dependence of the ring proton spectra of various *N*-substituted picramides in dichloromethane, and found that the energy barrier to rotation decreases markedly with increasing bulk of the alkyl substituent.

Nitrogen bases

Crampton and Gold[10] showed that in DMSO 1,3,5-trinitrobenzene reacts with primary and secondary aliphatic amines to give σ-complexes by attachment of

an amide ion at an unsubstituted ring position. Buncel and Webb[11] found that in the presence of aniline the 1,3,5-trinitrobenzene-methoxide adduct is converted to the anilide adduct **6** in which spin coupling was observed between the amino proton and the adjacent ring proton. Recently, Foster and Chudek[12] have reported the ^{1}H NMR spectra of a number of adducts



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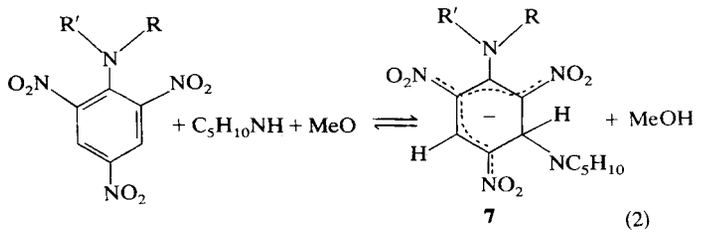
formed from polynitroaromatics in liquid ammonia. Particularly relevant to the present work is their observation that 1:1 and 1:2 adducts are formed from picramide and *N,N*-dimethylpicramide by amide ion addition at unsubstituted ring positions.

In continuation of our interest[13] in the relative affinities of nucleophiles for carbon (termed carbon basicity) and protons (proton affinity) we have examined the modes of interaction of *N*-substituted picramides with piperidide ions and benzylamide ions in DMSO containing *c.* 10% methanol.

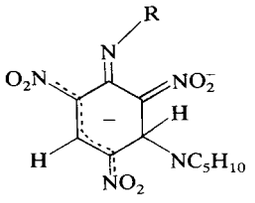
Addition of piperidine to solutions of *N*-methyl or *N,N*-dimethylpicramide in DMSO resulted in a shift to high field and considerable broadening of the ring proton resonance. The magnitude (up to 2.5 ppm) of the change in chemical shift indicates that as in the case of 1,3,5-trinitrobenzene[10] piperidide ion addition is occurring at a ring-carbon carrying hydrogen. The broadness of the peak results from moderately fast exchange of piperidide ions between substrate molecules. Sharper spectra were obtained by producing piperidide ions by addition of sodium methoxide in methanol [Eqn (2)]. They show that the major 1:1 interaction results in piperidide attack at the 3-position to give **7**. In the case of *N*-methylpicramide, mixtures were made up in DMSO containing a 1:1 ratio of parent and sodium methoxide; as the concentration of piperidine was increased to a ratio of 1:1:1 new bands at δ 5.68 and 8.53 increased in intensity at



7 (2)

the expense of those (mainly due to conjugate base) resulting from interaction of the parent with methoxide ions. The position of the high field band, δ 5.68, is characteristic[10] of ring protons adjacent to an aliphatic amide ion and indicates formation of **7** (R = Me, R′ = H). Bands in similar positions were produced (Table 7) from *N,N*-dimethylpicramide and from *N*-isopropyl- and *N*-*tert*-butylpicramide in mixtures of mole ratio 1 substrate:1 methoxide:1 piperidine. Hence the major 1:1 interaction of the piperidide ion results in C—N bond formation rather than in proton transfer.

In the cases of *N*-methyl, *N*-isopropyl- and *N*-*tert*butylpicramides there was evidence that 1:2 interaction resulted in transfer of the amino proton to give **8**. Thus, as the concentration of sodium methoxide was increased to a ratio of 1:2 no new bands were



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observed but the separation of the ring proton bands gradually increased. This is best interpreted as rapid interconversion of the adducts **7** and **8**. Similar spectra were observed with mole ratios of parent : piperidine : methoxide of 1:1:2 and 1:2:2. This does not necessarily imply that the 1:2 interaction of the piperidide ion involves proton transfer rather than base addition, since two sets of competing equilibria are involved and the magnitudes of the

$$C_5H_{10}NH + \mathbf{7} + MeO^- \rightleftharpoons \mathbf{8} + C_5H_{10}NH \quad (3)$$

$$\left\{\begin{array}{c} C_5H_{10}NH + MeO^- \rightleftharpoons \quad C_5H_{10}N^- + MeOH \\ C_5H_{10}N^- + \mathbf{7} \rightleftharpoons ? \end{array}\right\} \quad (4)$$

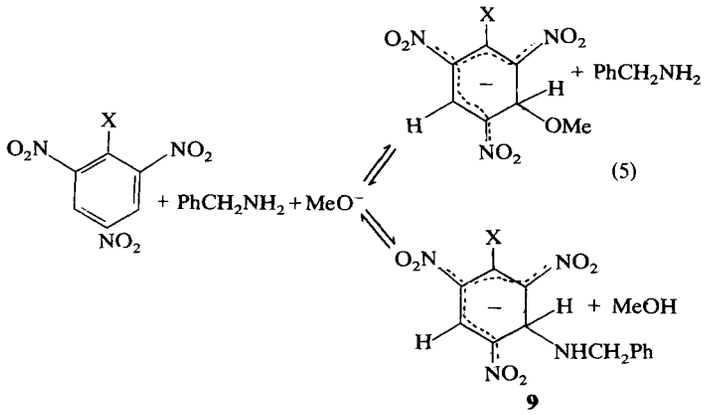
equilibrium constants will determine which wins. In Eqn (3) methoxide ion acts directly with **7** to give **8**. In Eqn (4) the formation of piperidide ion is followed by its interaction with **7**. The latter reaction might result in formation of **8** or alternatively in a di-adduct formed by piperidide attack at both the 3- and 5-positions.

The addition of benzylamine to solutions of the parent nitro-aromatics in DMSO caused a pronounced broadening and shift to high field of the ring proton resonances. Sharper spectra were obtained by generating the benzylamide ion by reaction with sodium methoxide. The usual reaction medium was DMSO-d_6-methanol 90/10 (v/v). The mole ratio of nitro compound to methoxide was kept at 1:1 and the spectral changes determined as the benzylamine concentration was increased. In each case the spectra indicated addition of benzylamide ion at unsubstituted ring positions. Thus, in the case of 1,3,5-

Table 7. Chemical shifts of ring protons of piperidide adducts

7		δ ring	
R	R′		
Me	Me	5.73	8.53
Me	H	5.68	8.53
Isopropyl	H	5.70	8.60
tert-But	H	5.73	8.55
8			
R			
Me		5.58	8.78
Isopropyl		5.50	8.75
tert-But		5.58	8.60

trinitrobenzene increasing the benzylamine concentration caused a decrease in the bands at δ 8.48 and 6.16 due to the methoxide adduct and an increase in intensity of bands at δ 8.37 and 5.72 due to the benzylamide adduct. Bands were observed at δ 3.50 (CH_2) and 7.18 (Ph) due to complexed benzylamine and at δ 3.73 and 7.30 due to free benzylamine. Conversion of the methoxide adduct to the benzylamide adduct is not complete in a solution containing an equimolar concentration of benzylamine, indicating that in our solvent system the equilibria of Eqn (5)



(5)

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are balanced. Chemical shifts are in Table 8. It is of interest that in each case the spectra of **9** show spin coupling of the amino proton of the added benzylamine group with the adjacent ring proton (J = 5 Hz) and with the methylene protons (J = 7 Hz). Measurements on instruments operating at 60 MHz and 90 MHz confirmed that the line separation was independent of the field. Further confirmation that the observed effect was due to spin coupling was obtained by carrying out measurements with benzylamine in which the amino protons had been exchanged for deuterium. The spectra obtained with the deuterated compound showed singlet bands at δ 5.7 and 3.5. The unusual observation of spin coupling in the present case has analogy with the observation[11] of coupling in the anilide adducts **6** and indicates that exchange of the amino proton in **9** is slow, possibly because of hydrogen bonding to the adjacent nitro group.

Table 8. Chemical shifts of benzylamide adducts 9

Structure 9 X	Ring protons[a]	CH_2[b]		*N*-Alkyl
H	8.37 5.72(d)	3.50(d)	7.18	
NH_2	8.50 5.71(d)	3.45(d)	7.15	
NHMe	8.40 5.69(d)	3.55(d)	7.22	2.90
$NHBu^t$	8.35 5.75(d)	3.65(d)	7.23	1.43 11.0(NH)
NMe_2	8.43 5.74(d)	3.65(d)	7.22	2.80

[a] High-field bands are doublets, J = 5 Hz.
[b] Doublet, J = 7 Hz.

EXPERIMENTAL

Picramide and its derivatives were prepared by reaction of 1-chloro-2,4,6-trinitrobenzene with the appropriate amine in methanol or aqueous methanol. Recrystallization from methanol yielded products with the following melting points: picramide 195 °C, lit.[14] 192–5 °C; *N*-methyl- 116 °C, lit.[14] 115 °C; *N*-isopropyl- 108 °C, lit.[14] 107 °C; *N*-*tert*-butyl- 95 °C, lit.[9] 95 °C; *N*,*N*-dimethyl- 139 °C, lit.[14] 138 °C. Sodium methoxide solutions were prepared by dissolving clean sodium in AnalaR methanol under nitrogen and were titrated with standard acid. Sodium isopropoxide solutions were similarly prepared from sodium and isopropanol. Piperidine and butylamine were commercial samples. Deuterated benzylamine ($PhCH_2ND_2$) was prepared by reaction of benzylamine with deuterium oxide; two exchange experiments yielded a product containing >95% of the required deuterated product. Dimethyl sulphoxide was dried over calcium hydride and fractionated under reduced pressure, the middle fraction being collected. DMSO-d_6 was a commercial specimen.

^{1}H NMR measurements were made at 60 MHz on a Varian A56/60 instrument at 35 °C or at 90 MHz on a Bruker HX 90E instrument (22 °C) modified for FT operation and using a deuterium lock, with pulsewidths of 10 μs, pulse delays of 1–2 s, and sweepwidths of 1200 Hz. All measurements were made relative to internal tetramethylsilane. The concentration of the nitro-aromatic compounds was approximately 0.2 mol l^{-1} and the solvent compositions are given in the text.

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