Kinetic Deuterium Solvent Isotope Effects in the Pyridine-catalysed Iodination of 2-Nitropropane in Aqueous and Methanolic Solutions

By **Victor Gold** * and **Kenneth P. Morris**, Department of Chemistry, University of London King's College, Strand, London WC2R 2LS

The rate of proton transfer from 2-nitropropane to pyridine was measured in the solvents H_2O, D_2O, CH_3OH, and CH_3OD by the observation of the rate of disappearance of added iodine at 25 °C. The reaction is *ca.* 150 times slower in methanol than in water, but the factor by which the rate constant is changed when hydroxylic protium is replaced by deuterium is slight and practically the same in both media (k_H/k_D *ca.* 1.05 ± 0.02). The result rules out from further consideration the idea that the marked difference in solvent isotope effects for the corresponding reactions of the same substrate with lyate ions in these two solvents is due to some general and unexplained solvent effect rather than to an effect specifically associated with the chemical differences between lyate ions in water and alcoholic media.

PROTON transfer reactions of the type represented by equation (1), where SH is a carbon acid and OR^- is a

$$SH + OR^- \longrightarrow S^- + ROH \qquad (1)$$

lyate ion (hydroxide, R = H, or alkoxide, R = alkyl), proceed more rapidly in a fully hydroxy-deuteriated solvent (ROD) than in light solvent (ROH).[1] In aqueous solutions the rate constants are typically in the ratio k_H/k_D 0.7—0.8, whereas in methanol and in other aliphatic alcohols this solvent isotope effect is more marked, with k_H/k_D *ca.* 0.43. If equation (1) were a complete representation of the rate-limiting step, solvent protons (or deuterons) would not be concerned in the reaction when R = alkyl, and no solvent isotope effect should be present in that case. However, a marked isotope effect is observed and solvent molecules must therefore play an additional role in the reaction, most plausibly by specific solvation of the lyate ion by hydrogen bonding, as in the formula $RO^-(HOR)_3$.[2,3] The smaller isotope effect in water can then be thought to arise in the main from the presence of the additional exchangeable proton in the HO^- grouping of $HO^-(HOH)_3$.

It is a corollary of this interpretation that the corresponding proton transfer to a less strongly hydrogen-bonded solute base (*e.g.* a tertiary amine) should show less pronounced solvent isotope effects, and there is experimental evidence in support of this. These conclusions are tested in the present study by an examination of reaction (2), of 2-nitropropane with pyridine, in H_2O,

$$(CH_3)_2CHNO_2 + Py \longrightarrow (CH_3)_2CNO_2^- + PyH^+ \qquad (2)$$

D_2O, CH_3OH, and CH_3OD as solvents. The reaction rate is conveniently observed by scavenging the anion with an iodinating agent, the concentration change of which is monitored.

The solvent isotope effect for the reaction of 2-nitropropane with lyate ion had previously been measured under comparable conditions (in methanol,[3b] k_H/k_D 0.74; in water,[3c] k_H/k_D 0.43). The kinetics of reaction (2) in aqueous solution were thoroughly studied by Bell and Goodall,[4] and in a mixed alcoholic solvent by Lewis and Funderburk.[5] The techniques developed by these groups of authors have been adapted to the present work.

Levin and Rappe have more recently reported kinetic deuterium solvent isotope effects of proton transfer reactions for several carbon acids in different alcoholic media.[6,7] These studies included two tertiary amines as bases. However, as was later appreciated,[7d] the use of unbuffered solutions of amines in methanol also leads to formation of methoxide ions according to equilibrium (3). Although there is some evidence that the con-

$$Et_3N + MeOH \rightleftharpoons Et_3NH^+ + MeO^- \qquad (3)$$

sequent possibility of reaction between the substrate and methoxide ions may not always be important,[8d] the interpretation of the measured isotope effects is subject to some uncertainty, since the value of the equilibrium constant of reaction (3) will change on going to MeOD as solvent. By use of buffered solutions a corresponding complication due to the hydrolysis of trimethylamine was avoided in a study of the solvent isotope effect on the rate of the ionization (measured as detritiation) of 1,4-dicyanobut-2-ene under the influence of triethylamine in aqueous solutions (k_H/k_D 1.24; the corresponding ratio for hydroxide ion as the base is 0.72).[8]

Our previous work [9] on the iodination of pentan-3-one in the presence of pyridine and 2,6-lutidine in aqueous buffered solutions showed solvent isotope effects (k_H/k_D) of a similar magnitude (1.20 and 1.22, respectively), but these measurements were not extended to alcoholic solutions. The present study, in conjunction with measurements of the solvent isotope on reactions with lyate ions, now permits a comparison of solvent isotope effects for a single substrate in alcoholic and aqueous medium with lyate ions and with a solute base, for a straightforward test of the hypothesis that the role of the solvent in proton transfer from a carbon acid to a lyate ion differs from the role of the solvent in the corresponding reaction involving a less strongly hydrogen-bonding solute base.

EXPERIMENTAL

2-Nitropropane (Koch-Light) was analysed by g.l.c. and was found to contain nitroethane (0.84 mole %), 1-nitropropane (2.1 mole %), acetone (0.02 mole %), and two other unidentified impurities in about the same concentrations as acetone. Spinning-band column distillation and preparative g.l.c. removed 1-nitropropane completely and reduced the nitroethane content to 0.6 mole %. The purified sample was used for experiments in methanol. The commercial product was employed for runs in aqueous solution where the role of reactive impurities was reduced in other ways (see below).

Pyridine (B.D.H. AnalaR) was found to react with I_2–KI in methanol. In order to remove the reactive impurity or impurities the sample (400 cm^3) was therefore refluxed for 1 h with iodine (5 g) and potassium iodide (2 g), followed by fractional distillation. This procedure was repeated, and the sample was then refluxed with calcium hydride for 1 h, again followed by fractional distillation. It was redistilled before use.

Methanol (Burroughs, A. R. quality) was allowed to stand over molecular sieve (3A) for several days and distilled. Methan[^{2}H]ol was stated by the suppliers (Fluorochem. Ltd.) to have been purified by fractional distillation and filtration on a column of molecular sieve and checked by g.l.c. and i.r. and n.m.r. spectroscopy (isotopic purity 99%): this sample and later ones from the same source were used without further treatment. N.m.r. analysis indicated a deuterium content >99.5%.

Deuterium oxide (Fluorochem or Prochem; 99% D) and a solution of deuterium chloride in deuterium oxide (Fluorochem) were used direct.

Sodium perchlorate (Hopkin and Williams) was freed from water of crystallisation by washing with acetone and drying (120°; 10 days). Other inorganic reagents were B.D.H. AnalaR products.

Kinetic Measurements on Aqueous Media.—A stock solution of pyridine was prepared from a weighed amount of base, partial neutralisation with hydrochloric acid (to [Py]/[PyH$^+$] 61.7) or, correspondingly, with DCl in D_2O, and addition of sodium perchlorate (to achieve an ionic strength of 0.2M in the reaction medium). A 3 cm^3 portion of this stock solution was transferred to the spectrophotometer cell in its thermostatted cell housing (at 25 °C). A few µl of a solution of 2-nitropropane and finally a solution of iodine in aqueous potassium iodide were added from µl syringes to start the reaction. The cell was shaken and the progress of the reaction was monitored by observation of the decrease in absorbance at 353 nm corresponding to consumption of tri-iodide according to the stoicheiometric equation (4). The overall concentration of iodine ($[I_2]^* =$

$$(CH_3)_2CNO_2^- + I_3^- \longrightarrow (CH_3)_2CINO_2 + 2I^- \quad (4)$$

$[I_2] + [I_3^-]$) was much smaller than that of the other reactants. For the main series of experiments a second addition of iodine solution could therefore be made at the end of each experiment for the same reaction solution at effectively the same concentration of 2-nitropropane. The disappearance of tri-iodide ion was monitored as before. It was reasoned that any highly reactive trace impurities would be iodinated in the first run, so that the rate constants obtained for the second addition of iodine should be more reliable. In fact, a slight reduction in rate was observed in all cases, and the rate constants quoted in Table 1 are those for the second runs. However, the solvent isotope effects did not show a significant change, presumably because the solvent isotope effect for iodination of the reactive impurity is similar to that for 2-nitropropane. This is relevant, because double additions proved impracticable for experiments with methanol. The concentration of tri-iodide ion can be related to the overall concentration of iodine, using Awtrey and Connick's value for the stability constant of the ion,[10] by expression (5). The tri-iodide ion was found to

$$[I_3^-] = 710\,[I_2][I^-] = 710\,[I_2]^*[I^-]/(710[I^-] + 1) \quad (5)$$

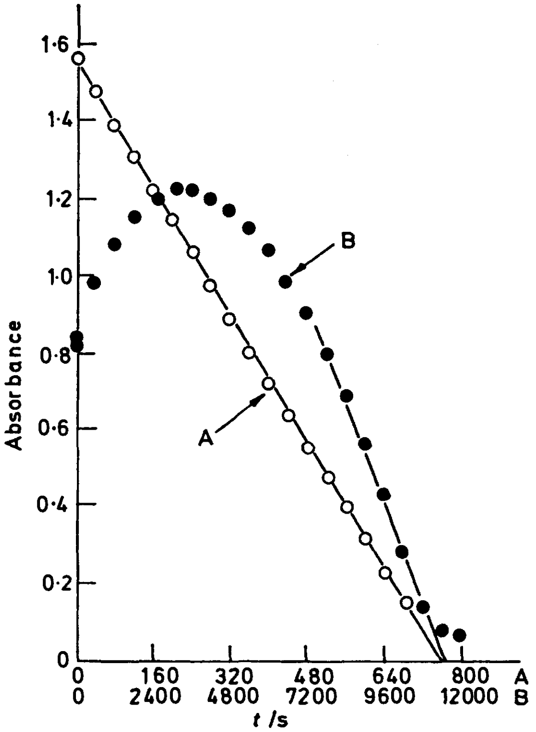
obey Beer's law at 353 nm; its molar absorption coefficient (extinction coefficient ε) was determined as 2.44 × 10^4 dm^3 mol^{-1} cm^{-1}. The general procedure, with minor modifications, is due to Bell and Goodall,[4] who explain the reasons for the choice of concentrations. We confirmed that pyridine, even at concentrations exceeding those used in kinetic experiments, does not affect the light absorption due to the tri-iodide ion.

TABLE 1

Reaction of 2-nitropropane with pyridine in aqueous solution. [2-nitropropane] 5.68 × 10^{-3}M

		[Pyridine]/M	$-10^8 \frac{d[I_2]^*}{dt}$ /dm^{-3} mol s^{-1}
A	In H_2O	0.150	1.70
		0.247	2.75
		0.348	3.51
		0.446	4.77
		0.550	5.38
		0.644	6.24
B	In D_2O	0.152	1.85
		0.251	2.73
		0.352	4.03
		0.450	4.45
		0.656	5.41

Provided the formation of 2-iodo-2-nitropropane from the anion $(CH_3)_2CNO_2^-$ is a rapid process, the observed rate of disappearance of iodine species from the solution will be determined by the rate of reaction (2). Since 2-nitropropane is in large excess over iodine, the reaction should



Specimen kinetic runs: A, experiment in aqueous solution, [Py] 0.2468, [PyH$^+$] 0.004, $[I_2]_0$ 6.87 × 10^{-5}, [2-nitropropane]$_0$ 0.016 48, $[KI]_0$ 0.019 94, [$NaClO_4$] 0.177 0M; B, experiment in methan[^{2}H]ol solution, [Py] 1.00, [PyD$^+$] 0.0162, $[I_2]_0$ 1.52 × 10^{-4}, [2-nitropropane]$_0$ 0.908, [$NaClO_4$] 0.0838, [D_2O] 0.338M then follow zeroth-order kinetics. In practice, the concentration of I_3^- falls linearly with time over almost the entire course of the reaction (see Figure) but tails off more gradually towards the end. This rate decrease does not interfere with the evaluation of the zeroth-order rate constant. It arises from the slowing down of the scavenging of the anion at low concentrations of iodine species and is minimised by keeping the concentration of iodide fairly low, so that an appreciable proportion of the overall iodine concentration remains in the form of free iodine, a more reactive species than tri-iodide ion.

The observed zeroth-order rate constants ($-d[I_2]^*/dt$) were corrected for the slow consumption of iodine species in the absence of 2-nitropropane (evaluated from blank experiments at each pyridine concentration at an overall iodine concentration of two-thirds times the initial value in experiments with 2-nitropropane). The corrected rate, corresponding to disappearance of iodine species due to their reaction with the conjugate base of 2-nitropropane, contains contributions from the reactions of all bases present in solution with 2-nitropropane, according to equation (6).

$$-d[I_2]^*dt = (k_{Py}[Py] + k_{OH}[OH^-] + k_0)[2\text{-NP}] \quad (6)$$

The second and third terms in parentheses are small in comparison with the required first term. From the values of k_{OH} and k_O given by Bell and Goodall[4] we calculate processes not involving pyridine to contribute just over 1% to the total rate: they are accordingly not significant in our experiments in aqueous solution. For deuterium oxide solutions the corresponding correction terms are not known.

The method of evaluating results adopted in practice avoided the use of such calculated corrections. Equation (6) implies that for a series of kinetic experiments at a constant buffer ratio, the sum $(k_0 + k_{OH}[OH^-])[2\text{-NP}]$ represents a small intercept on the linear plot of observed rate against pyridine concentration. The catalytic coefficient k_{Py} was therefore obtained as the slope of this regression line.

In an independent series of experiments at constant pyridine concentration, it was verified that the reaction rate was strictly proportional to the concentration of 2-nitropropane.

Results are summarised in Table 1. The data points for aqueous solution are represented by equation (7) and those for solutions in deuterium oxide by equation (8). The

$$-d[I_2]^*/dt = 10^{-8}\,(0.41 + 9.17\,[Py])\ \text{dm}^{-3}\text{mol s}^{-1} \quad (7)$$

$$-d[I_2]^*/dt = 10^{-8}\,(0.60 + 8.79\,[Py])\ \text{dm}^{-3}\ \text{mol s}^{-1} \quad (8)$$

corresponding second-order rate constants, obtained by dividing the numerical coefficient of the second term by the concentration of 2-nitropropane, are 1.62×10^{-5} and 1.55×10^{-5} dm^3 mol^{-1} s^{-1}, respectively. Accordingly, the value of the isotope rate ratio k_{H_2O}/k_{D_2O} is 1.04. The value 1.62×10^{-5} dm^3 mol^{-1} s^{-1} is in reasonable agreement with Bell and Goodall's corresponding result[4] (1.74×10^{-5} dm^3 mol^{-1} s^{-1}).

Kinetic Measurements on Methanol Solutions.—Two major differences in behaviour were found in this solvent. First, the rate constant for reaction (2) was much smaller: a higher concentration of pyridine was therefore used so that the same basic procedure should be applicable in both media. Second, the presence of iodide, even at a low concentration, depressed the completion of reaction (4) (probably by a mass law effect) to such an extent that the absorbance at 380 nm did not decrease linearly with time over an adequate proportion of the reaction. The reactions were accordingly carried out without the addition of iodide. However, since iodide is formed during the reaction of iodine with the carbanionic product of reaction (1), the apparent extinction coefficient for the iodine species increases as the reaction progresses. As a result the observed absorbance increases during the early stages of the reaction, passes through a maximum, and then decreases. There is a short linear portion of the curve before the final tailing-off (Figure). The rate of iodine consumption was accordingly determined by measuring the time required for the absorbance to fall from its initial value, immediately after the addition of iodine, to zero (as determined by extrapolation of the linear portion), and dividing the initial concentration of iodine by this time. The procedure is justified in view of Lewis and Funderburk's demonstration,[5] for this reaction in a related solvent system (t-butyl alcohol–water), that an absorbance–time curve of the shape described corresponded to a linear decrease in the overall concentration of iodine. Blank rates, in the absence of substrate, were measured at the highest concentration of pyridine employed. The slow increase in absorbance corresponded to a correction of $<1\%$ of the observed rate, which was negligible.

A weighed amount of pyridine was partially neutralised with a small volume (0.152—0.153 cm^3) of concentrated hydrochloric acid or of a solution of DCl in D_2O (to $[Py]/[PyH^+]$ or $[Py]/[PyD^+]$ 61.7). Sodium perchlorate was added to give an ionic strength of 0.1M after making the solution up to a fixed total volume with methanol or methan[^{2}H]ol. Reactions were initiated by injection of a small volume of 2-nitropropane into the solvent in the thermostatted cuvette. Values of k_{Py} were evaluated from the regression of observed rate constants on pyridine concentration (up to 2.0M) (Table 2).

TABLE 2

Reaction of 2-nitropropane with pyridine in methanol solution. [2-nitropropane] 0.0908M

	$-\dfrac{10^8\,d[I_2]^*}{dt}$ /dm^{-3} mol s^{-1}	
[Pyridine]/M	In CH_3OH	In CH_3OD
0.50	0.685	0.807
1.00	1.22	1.33
1.50	1.69	1.79
2.00	2.23	2.25
2.50	2.57	2.55
3.00	3.02	2.96
3.50	3.02	2.85
4.00	3.16	3.23
4.50	3.30	3.11

A strictly linear dependence on pyridine concentration was observed up to a concentration of 2.0M, beyond which the rate increased less rapidly and rate constants were less reproducible. The technique of using successive injections of substrate in order to remove reactive impurities from 2-nitropropane was found unsatisfactory in this solvent, possibly because of the effect of iodide produced in the reaction. To correct for the presence of 0.60% nitroethane in the sample of 2-nitropropane, values of rate constants should be reduced by 4.2% if the correction established by Bell and Goodall[5] for the same effect in water is applicable. Since the same specimen of 2-nitropropane was used in all experiments, any inadequacy of this correction is expected to be quite negligible in the values of the isotopic rate ratios.

The first four data points in columns 2 and 3 of Table 2 satisfy equations (9) and (10). Accordingly, the isotopic rate ratio for reaction with pyridine, $k_{\mathrm{MeOH}}/k_{\mathrm{MeOD}}$, has the value 1.06. The two second-order rate constants for the reaction of pyridine with 2-nitropropane then have the

$$-\mathrm{d}[\mathrm{I}_2]^*/\mathrm{d}t = 10^{-8}\,(0.183 + 1.018\,[\mathrm{Py}])\ \mathrm{dm}^{-3}\ \mathrm{mol\ s}^{-1}\ (\text{in } \mathrm{CH_3OH}) \qquad (9)$$

$$-\mathrm{d}[\mathrm{I}_2]^*/\mathrm{d}t = 10^{-8}\,(0.348 + 0.956\,[\mathrm{Py}])\ \mathrm{dm}^{-3}\ \mathrm{mol\ s}^{-1}\ (\text{in } \mathrm{CH_3OD}) \qquad (10)$$

values 1.12×10^{-7} and 1.05×10^{-7} dm^3 mol^{-1} s^{-1} in MeOH and MeOD, respectively. Application of the 4.2% correction mentioned above would reduce these values to 1.07×10^{-7} and 1.01×10^{-7} dm^3 mol^{-1} s^{-1}, respectively.

DISCUSSION

The deuterium solvent isotope effects for the reaction of 2-nitropropane with pyridine in methanol ($k_{\mathrm{H}}/k_{\mathrm{D}}$ 1.06) and in water ($k_{\mathrm{H}}/k_{\mathrm{D}}$ 1.04) are not significantly different, and are both close to unity, although the rate constants themselves differ by a factor of the order of 150. In both respects this behaviour stands in contrast to the ionisation of 2-nitropropane in the presence of lyate ions for which the rate constants are almost the same in methanol and in water but for which the solvent isotope effects in methanol ($k_{\mathrm{H}}/k_{\mathrm{D}}$ 0.74) and in water ($k_{\mathrm{H}}/k_{\mathrm{D}}$ 0.43) have very different values. It is therefore inferred that the solvent isotope effects observed with alkoxide ions have their origin in the strong and extensive hydrogen bonding of these species, a feature which is much less important in solutions of pyridine. The absence of a pronounced isotope effect with pyridine (which confirms measurements with amine bases on other reactions for which comparative data with lyate bases are not available) seems to rule out from further consideration the possibility that more general solvent isotope effects of unspecified origin affect proton transfer processes of this type.

The difference in the rate constants for the reaction with pyridine in the two solvents is consistent with the separation of electric charges that occurs in the transition state for reaction (2). Such a reaction is expected to proceed more slowly in the less polar solvent methanol. By contrast, electric charges are conserved in reaction (1), but the solvent change is also associated with a change in the base (from hydroxide to methoxide ion). The apparent absence of a solvent influence on the rate may consequently be due to some cancellation of opposed effects.

The small solvent isotope effects observed with pyridine are interpreted in terms of the mechanism (11) and (12) (up to the transition state) according to which

$$\mathrm{Py}\cdots\underset{(1)}{\mathrm{HOR}} \overset{\text{rapid}}{\rightleftharpoons} \mathrm{Py} + \mathrm{HOR} \qquad (11)$$

$$\mathrm{Py} + \underset{(2)}{\mathrm{SH(HOR)}_s} \longrightarrow \left[\overset{\delta+}{\mathrm{Py}}\cdots\mathrm{H}\cdots\overset{\delta-}{\mathrm{S}}\cdots\underset{(3)}{(\mathrm{HOR})_m}\right]^{\ddagger} \qquad (12)$$

equation (13) results where ϕ_1—ϕ_3 are fractionation factors of the exchangeable hydrogen atoms indicated by the respective numerals in equations (11) and (12).

Because rates of proton transfers of this type are known to be sensitive to steric effects, it has been concluded that the transfers must be 'direct', as is implied

$$\frac{k_{\mathrm{H}}}{k_{\mathrm{D}}} = \frac{\phi_1\phi_2{}^s}{\phi_3{}^m} \qquad (13)$$

in equation (9) (and *not* via a solvent bridge between pyridine and the carbon acid).[11]

The dissection of the formation of the transition state into two steps is chemically plausible: the result of equation (13) would not be altered by the less probable assumption that these two processes are merged. Since the incipient negative charge in the transition state will be mainly located on the oxygen atoms of the nitro-group, the existence of hydrogen bonding (with a resultant fractionation factor in the hydrogen-bonding atoms of solvent molecules $\phi_3 < 1$) is expected. Whilst ϕ_3 will probably not be much less than unity, this fractionation seems slightly to outweigh ϕ_1 and ϕ_2, since $k_{\mathrm{H}}/k_{\mathrm{D}} > 1$. The inference that hydrogen bonding to the uncharged reactants is less important than that to the incipient anionic sites is perhaps not unexpected. However, all these effects are very small, and that is our main conclusion. The elaboration of details may be further complicated by the conclusion, on the basis of large primary (substrate) isotope effects, that the proton transfer from 2-nitropropane to pyridine shows significant characteristics of tunnelling.[4,5] Consequently, the change in hydrogen bonding (to the nitro-group), accompanying formation of the anion, may lag behind the proton jump, with a resultant attenuation of the fractionation effects associated with the transition state.

The observation of very similar solvent isotope effects with pyridine in water and in methanol leads inevitably to the conclusion that the pronounced difference between the isotope effects in the two solvents observed for lyate catalysis is directly associated with the chemical differences between aqueous hydroxide and methanolic methoxide ions. Whatever the detailed explanation of the large difference in solvent isotope effects may be, it cannot be ascribed to some general isotopic medium effect of unexplained origin.

[0/071 *Received*, 14*th January*, 1980]

REFERENCES

[1] P. M. Laughton and R. E. Robertson, in 'Solute–Solvent Interactions', eds. J. F. Coetzee and C. D. Ritchie, Dekker, New York, 1979.

[2] R. A. More O'Ferrall, *J. Chem. Soc.* (*B*), 1969, 114; 1970, 268.

[3] V. Gold and S. Grist, (*a*) *J. Chem. Soc.* (*B*), 1971, 1665; (*b*) *ibid.*, p. 2282; (*c*) *J.C.S. Perkin II*, 1972, 89.

[4] R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, **A294**, 273.

[5] E. S. Lewis and L. H. Funderburk, *J. Amer. Chem. Soc.*, 1967, **89**, 2322; see also E. S. Lewis and J. D. Allen, *ibid.*, 1964, **86**, 2022.

[6] J.-O. Levin and C. Rappe, *Chem. Scripta*, 1971, **1**, 233.

[7] J.-O. Levin (*a*) *Chem. Scripta*, 1973, **4**, 85; (*b*) *ibid.*, 1974, **6**, 89; (*c*) 'Experimental Studies of Kinetic Solvent Deuterium Isotope Effects on Proton Abstraction in Alcohol Solutions', Umeå, 1974; (*d*) *Chem. Scripta*, 1975, **7**, 54.

[8] E. A. Walters and F. A. Long, *J. Phys. Chem.*, 1972, **76**, 362.

[9] J. P. Calmon, M. Calmon, and V. Gold, *J. Chem. Soc.* (*B*), 1969, 659.

[10] A. D. Awtrey and R. I. Connick, *J. Amer. Chem. Soc.*, 1951 **73**, 1842.

[11] J. A. Feather and V. Gold, *J. Chem. Soc.*, 1965, 1752.