Non-anomalous Nucleophilic Reactivity of Carbanions towards the Nitroso Group

J. Ramón Leis,* M. Elena Peña and Ana Ríos
Departamento de Química Física, Facultad de Química, Universidad de Santiago, 15706 Santiago de Compostela, Spain

The reactivities of a series of carbanions (several enolate and nitronate ions and the diethyl malonate anion) with the nitroso groups of *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide and a variety of alkyl nitrites have been studied. The reactivity of the carbanions correlates well with their basicity over 8 pK_a units. Nitronate ions are only slightly less reactive (less than a factor of 10) than enolates of similar basicity. In general, the reactivities of the carbanions are similar to those of secondary amines of similar basicity, which contrasts with their anomalous behaviour in other chemical reactions (especially protonation processes). The causes of this non-anomalous behaviour are discussed.

Though *C*-nitrosation of aliphatic compounds has long been used in syntheses,[1] detailed studies of the mechanism of this process have only recently been carried out (largely by Williams and coworkers).[2-9] This work has chiefly involved nitrosation in acid media by the strong electrophiles obtained by protonation of nitrous acid (NO^+ or $H_2NO_2{}^+$, ONCl, ONBr, *etc.*). It is found that, if allowed by their structure, the *C*-nitroso-compounds initially formed undergo tautomerization to the more stable oxime. The reaction is analogous to other electrophilic substitutions, and there is evidence that for ketones and other carbonylic substrates, it occurs *via* the enol tautomer,[2,7-9] while for nitro compounds it generally occurs *via* the corresponding nitronic acid.[6] In some cases, however, kinetic studies have revealed the involvement of enolates or carbanions as the effective substrate,[3,5,7,8] and this is in fact the only route detected for malononitrile.[4]

Aliphatic *C*-nitroso compounds can also be prepared in basic media with alkyl nitrites as nitrosating agents.[1] This reaction is presumably due to the nucleophilic character of carbanions and enolates, but as far as we know there have been no kinetic studies of its mechanism. One reason for this lack of information may be related to the complexity of the behaviour exhibited by carbanions in the few kinds of reaction in which their reactivity has been studied, especially in water. In fact, the term 'pseudobases' has been applied to carbanions on account of their abnormally low reactivity with protons and ordinary acids.[10-14] Corresponding 'anomalies' are observed in the deprotonation of carbon compounds by bases. The absence of correlation between basicity and reactivity, especially striking in the case of different families of carbanions, and even, in the well documented case of nitroalkanes, the existence of negative correlation (Brønsted exponents outside the classical range 0–1) throws doubt on the validity and interpretation of free energy correlations and prevents identification of the Brønsted exponent with the degree of proton transfer that occurs in the transition state whatever the reason for such behaviour may be.[15-18]

To investigate these issues, we undertook a kinetic study of the reactivities of various carbanions with a structurally diverse series of alkyl nitrites and with *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide, which, like alkyl nitrites,[19] can transfer the nitroso group directly to a variety of nucleophiles (amines, azide, *etc.*) probably by a concerted mechanism. Our results throw light on the factors controlling the 'anomalous' reactivities of carbanions.

Experimental

Materials.—*N*-Methyl-*N*-nitrosotoluene-*p*-sulfonamide (MNTS) was purchased from Merck and used without further purification. Alkyl nitrites (2-ethoxyethyl, 2-chloroethyl, 2-bromoethyl and 2,2-dichloroethyl nitrite) were prepared by reaction between sodium nitrite and the corresponding alcohol in an acidic medium,[20] and were stored at low temperature in the presence of molecular sieves (to prevent water-catalysed hydrolysis); their identity was confirmed by ^1H NMR spectroscopy. Ketones and nitro compounds (from Aldrich) were purified by low-pressure distillation or recrystallization following standard procedures.[21] D_2O (99.77% D) was supplied by CIEMAT (Spain). All other reagents were Aldrich products used without further purification.

Solutions of MNTS, which is poorly soluble in water, were prepared in dioxane, and a small volume of these solutions was the last component added to reaction mixtures. A similar procedure was used for alkyl nitrites, aqueous solutions of which are unstable.[22] In each case, the percentage of dioxane in the final reaction mixtures (generally 10%) is indicated in the results tables below.

Methods.—For conventional kinetic experiments and VIS–UV spectra, Kontron Uvikon 930 or Spectronic 3000 diode array spectrophotometers were used, both with multiple cell carriers thermostatted by circulating water. For fast reactions ($t_{\frac{1}{2}}$ < 20 s), a Beckman DU-65 spectrophotometer recording up to 10 readings per second was used in conjunction with a Hi-Tech rapid mixing device; a solution of alkyl nitrite in a low concentration carbonate buffer (in which alkyl nitrites are reasonably stable)[22] was placed in one syringe, and the remaining components of the reaction mixture in the other. For fast reactions, kinetics were recorded in triplicate and the results averaged.

HPLC was performed with Beckman System Gold apparatus, using a UV–VIS detector (wavelength 250 nm). A Beckman Reverse Phase 5 μm Ultrasphere C18 column was used for both identification of reaction products and kinetic experiments. Concentrations were determined from electronically integrated peak areas.

pH was measured with a Radiometer PHM 82 pH-meter equipped with a GK2401B combined glass electrode.

^1H NMR spectra were recorded at room temperature on a Bruker WM250 apparatus operating at 250 MHz.

Kinetic Experiments.—All kinetic experiments were carried out at 25 °C. In most cases, the increasing absorbance due to formation of the reaction products was followed. The reaction spectra were generally clean, with no signs of kinetic complications; the only exception was the reaction with dimedone (see Results). Particular care was taken to check that the aggregation or decomposition of carbanions was not significant under the experimental conditions used. In some cases slow decomposition of the reaction product was detected, but this did not compete with the process under study. The isolation method was used for all the kinetic experiments, the concentration of nitrosatable substrate being very much in excess of that of the alkyl nitrite or MNTS (typically 10^{-3}–10^{-4} mol dm^{-3}). First-order integrated equations were in all cases fitted with great precision to the absorbance–time data. The corresponding observed first-order pseudoconstant shall be referred to below as k_0. Values of k_0 were always reproducible to within 3%.

When using buffers, in order to guarantee the desired pH at all substrate concentrations, the required quantities of buffer solutions were added to reaction mixtures which already contained the quantity of NaOH necessary to achieve the desired pH.

(a) *Pentane*-2,4-*dione*. The spectra of the reaction between this diketone and MNTS or the alkyl nitrites were clean, with clear isosbestic points at 365 and 410 nm in the case of reaction with MNTS. All these reactions were followed by recording the increase in absorbance at 430 nm due to formation of the reaction product. The diketone solution itself, with appropriate quantities of NaOH added, acted as a buffer to control the pH of the reaction mixture.

(b) *Indan*-1,3-*dione and Meldrum's acid* (2,2-*dimethyl*-1,3-*dioxane*-4,6-*dione*). Since nitrosation of indan-1,3-dione was much slower than that of pentane-2,4-dione, only the reaction with the most reactive alkyl nitrite, 2,2-dichloroethyl nitrite, was studied. Since this nitrite is unstable, especially at pH < 9, kinetics were studied in 0.0167 mol dm^{-3} carbonate/bicarbonate buffer of pH 9.91, at which pH the ketone is entirely in the enolate form. The spectrum of the reaction was clean, with a clear isosbestic point at 380 nm. Kinetics were followed by recording the increase in absorbance at 335 nm due to the product formation.

A similar situation was encountered with Meldrum's acid, the nitrosation of which by 2,2-dichloroethyl nitrite was followed at 320 nm in 0.5 mol dm^{-3} carbonate/ bicarbonate buffer of pH 9.71.

(c) 3-*Methylpentane*-2,4-*dione*. Study of the nitrosation of this ketone was hampered by its being unstable in basic media, as was found under various experimental conditions. Because of this, the only nitrosating agents used were MNTS and 2-ethoxyethyl nitrite (for which kinetics were followed at 358 and 378 nm respectively), and first-order rate equations could only be fitted satisfactorily when the reaction was fast enough for competitive decomposition of the substrate to be negligible (at substrate concentrations greater than 0.08 mol dm^{-3}). The experiments were performed at pH 10.5, at which only 25% of the substrate is in the enolate form, in the presence of sufficient NaOH to neutralize 25% of the substrate.

(d) *Dimedone* (5,5′-*dimethylcyclohexane*-1,3-*dione*) *and* 1,1,1-*trifluoropentane*-2,4-*dione*. Because of the complications encountered in the nitrosation of dimedone (see Results), the only nitrosating agent used was MNTS, and the kinetics of the reactions were studied by following the fall in MNTS concentration by HPLC. Volumes of 20 mm^3 of a thermostatted reaction mixture containing MNTS and excess dimedone at pH 6.32 (maintained by the buffering capacity of dimedone at this pH) were analysed at successive times using 50:50 (v:v) CH_3OH/H_2O as mobile phase at a flow rate of 2 cm^3 min^{-1}. A similar procedure was used to investigate the possible nitrosation of 1,1,1,trifluoropentane-2,4-dione.

(e) *Diethyl malonate*. To prevent hydrolysis of the substrate at high pH, reactions were carried out in 0.33 mol dm^{-3} carbonate/bicarbonate buffer of pH 9.71. Even so, only the reaction with 2,2-dichloroethyl nitrite was fast enough to avoid interference from the competing substrate hydrolysis reaction.

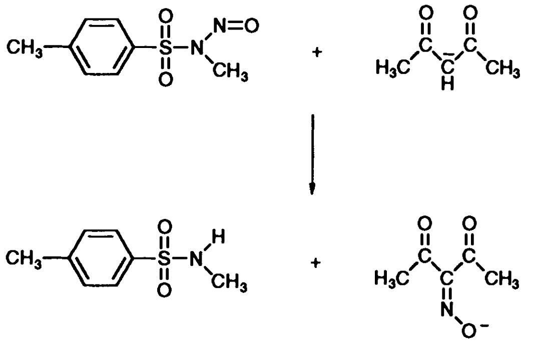
(f) *Nitro compounds*. The nitrosation of 1-nitropropane by MNTS and various alkyl nitrites was studied at pH 10.27 (maintained by using mixtures that were 5% nitro compound and 95% nitronate anion, with the concentrations of both > 10 times that of the nitrosating agent). No decomposition of the nitro compound/nitronate mixtures was observed during periods of several hours. However, the reaction between 1-nitropropane and 2,2-dichloroethyl nitrite was carried out at pH 9.91 in carbonate buffers, since the concentrations of 1-nitropropane used were otherwise insufficient to guarantee constant pH. Reaction kinetics were followed at 380–385 nm. For 1-nitroethane, totally neutralized nitro compound solutions had to be used to prevent significant decomposition; only the reaction with MNTS was studied.

(g) *Hydrolysis of alkyl nitrites*. When necessary, the rate of hydrolysis of alkyl nitrites in buffer solutions[22] was determined spectrophotometrically by following the disappearance of the alkyl nitrite at 250 nm. In all such cases, the absorbance–time data were fitted well by first-order integrated equations.

Results

Reaction Products.—The reaction of alkyl nitrites with carbonyl compounds in basic media generally results in *C*-nitrosation of the latter at activated sites,[1] after which the nitroso compound, if its structure allows, undergoes fast tautomerization to the more stable corresponding oxime, which at basic pH exists in its oximate form. As far as we know, there are no previously published references to this nitrosation reaction being carried out with the bidentate electrophile MNTS,[19a] whose S and nitroso N atoms might compete for the nucleophilic substrate. In this work, identification of reaction products therefore centred chiefly on the reaction with MNTS, which presents the advantage of its high stability. It was found that all the carbanions reacted with the MNTS NO group.

The nitrosation of pentane-2,4-dione by the four alkyl nitrites or MNTS led to the formation of the anion of 3-oximinopentane-2,4-dione[1] in quantitative yield, as shown by the final VIS–UV spectra of reaction mixtures being identical to each other and to those of oxime prepared from nitrous acid by conventional procedures[1,2] and brought to the working pH of the kinetic experiments. For the reactions with MNTS and 2-ethoxyethyl nitrite, the identity of the product was confirmed by HPLC, and for MNTS HPLC was also used to confirm the formation of *N*-methyltoluene-*p*-sulfonamide in > 96% yield under the working conditions of the kinetic experiments [eqn. (1)].



(1)

Similar identification procedures were carried out for the reaction with the representative nitro compound 1-nitropropane as substrate. Regardless of whether MNTS or alkyl nitrite was used as nitrosating agent, the product was the anion of propyl nitrolic acid. The reaction with MNTS involved only the nitroso group, HPLC showing a 97% yield of *N*-methyltoluene-*p*-sulfonamide under typical reaction conditions.

The nature and stability of the products of the nitrosation of

Table 1 First-order pseudoconstants k_0 for the nitrosation of pentane-2,4-dione in basic media containing 20% of dioxane; T = 25 °C

pH	[pentane-2,4-dione$_{tot}$]/mol dm^{-3}	k_0/s^{-1}
9.29	6.49×10^{-2}	8.62×10^{-4}
9.29	0.130	1.62×10^{-3}
9.29	0.195	2.54×10^{-3}
9.29	0.260	3.35×10^{-3}
9.29	0.325	4.13×10^{-3}
9.29	0.422	5.35×10^{-3}
9.29	0.519	6.18×10^{-3}
8.13	0.325	6.52×10^{-4}
8.22	0.325	7.74×10^{-4}
8.67	0.325	1.70×10^{-3}
9.00	0.325	2.93×10^{-3}
9.29	0.325	4.13×10^{-3}
9.36	0.325	4.41×10^{-3}
9.49	0.325	5.03×10^{-3}
9.61	0.325	6.79×10^{-3}

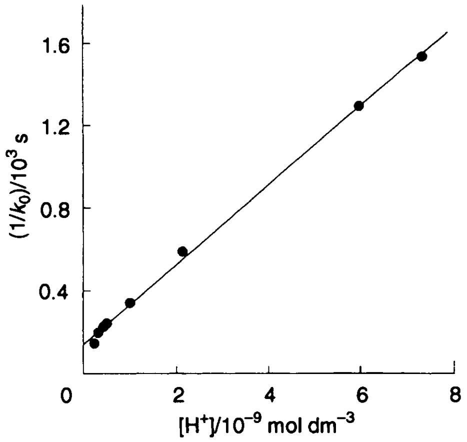


Fig. 1 Linearization of k_0–[H$^+$] data for the nitrosation of pentane-2,4-dione by MNTS [according to eqn (2)]; [pentane-2,4-dione$_{tot}$] = 0.325 mol dm^{-3}; 20% dioxane; T = 25 °C

dimedone were more problematic. In carbonate buffers of pH 9.7, reaction between MNTS or alkyl nitrite (*ca.* 2×10^{-3} mol dm^{-3}) and excess dimedone (*ca.* 0.2 mol dm^{-3}) gave a violet product (λ_{max} = 554 nm in 10% dioxane) *via* a process exhibiting complex, non-exponential absorbance–time records. When the initial reaction rate was increased by use of considerably higher concentrations of the most reactive alkyl nitrite (2,2-dichloroethyl nitrite) or MNTS, the mixture of products was initially an intense blue (λ_{max} = 585 nm in 10% dioxane), but the slow evolution of the visible absorbance band to shorter wavelengths suggested conversion to the violet product. As a first step towards the identification of these products, the expected oximate was prepared by a conventional nitrosation reaction.[23] When brought to basic pH, the resulting oxime solution turned deep blue,[23] exhibiting a spectrum similar to that of the blue solution mentioned above; the sodium salt of the oximate was isolated as a blue solid that was recrystallized from alcohol/water mixtures (λ_{max} = 589 nm, ε = 55.1 dm^3 mol^{-1} cm^{-1} in water), and its identity was confirmed by ^{1}H NMR spectrometry in D_2O [δ = 0.88 (s, 6 H), 2.25 and 2.47 (br, 4 H)]. The blue reaction product initially obtained upon nitrosation of dimedone with MNTS or alkyl nitrite in basic media therefore seems to be the expected oximate. However, attempts to isolate this product from the reaction mixtures failed because of conversion to the violet product during concentration (whether in a rotatory evaporator or under high vacuum at room temperature). These findings strongly suggest that the expected oximate is the initial product of the reaction studied, but is unstable under the reaction conditions, evolving (perhaps through reaction with excess dimedone) to the unidentified violet compound. Overlap between these two processes complicates the absorbance–time data.

Kinetic Studies

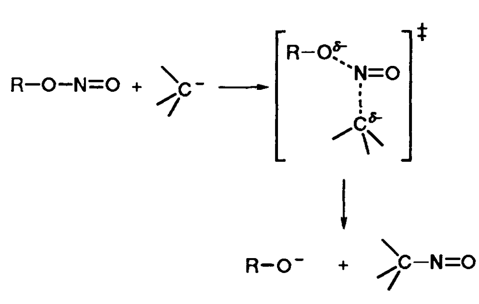
Most of the reactions studied were carried out without control of ionic strength, which preliminary experiments had shown not to affect the reaction rates (a characteristic common to other reactions between nucleophiles and alkyl nitrites[24] or MNTS[19]).

Nitrosation of Carbonyl Compounds.—(a) *Pentane*-2,4-*dione*. Table 1 lists the first-order pseudoconstants observed when pentane-2,4-dione was nitrosated by MNTS (*a*) at pH 9.29, with various total substrate concentrations ([enolate] + [ketone] + [enol]); and (*b*) at various pH values, with a constant total concentration of substrate. These results show the reaction to be of first order with respect to the substrate, while the increase in reaction rate with pH suggests that the enolate is the only reactive form of the substrate, eqn. (2) where K_{ap} is the apparent

$$k_0 = \frac{kK_{ap}[\text{substrate}_{tot}]}{K_{ap} + [\text{H}^+]} \tag{2}$$

acidity constant of pentane-2,4-dione, *i.e.* K_{ap} = [enolate][H$^+$]/([enol] + [ketone]). As predicted by eqn. (2), plotting $1/k_0$ against [H$^+$] affords a straight line (see Fig. 1), the slope and intercept at the origin of which imply that pK_{ap} = 9.14, in good agreement with the value determined potentiometrically by us and with previously published values.* The value of the bimolecular rate constant k for this reaction, 2.2×10^{-2} dm^3 mol^{-1} s^{-1}, is listed in Table 2 together with the corresponding values for nitrosation by the alkyl nitrites used.

With MNTS as nitrosating agent, experiments to determine the solvent isotope effect k(H)/k(D) afforded a value of 0.9, similar to those measured for *N*-nitrosation by MNTS,[19b] for which a simple concerted mechanism is postulated.[19] With 2-ethoxyethyl nitrite, however, the value of k(H)/k(D) was 1.7, similar to those observed for the reactions of alkyl nitrites with amines and the azide ion. In spite of suggestions[25] that this value might reflect a concerted mechanism combining the attack by the nucleophile with protonation of the alkoxide leaving group in the slow step, it seems more readily explained by the transition state shown in Scheme 1:[19b] if the oxygen atom is negative enough, it may be involved in strong hydrogen bonding to water molecules, resulting in fractionation factors[26]



Scheme 1

---

* A value of 9.08 for the pK_{ap} of pentane-2,4-dione is derived from the pK_a = 9 for the keto form (R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 1953, **75**, 2439), using a value of 0.2 (A. S. N. Murthy, A. Balasubramanian, C. N. R. Rao and T. R. Kasturi, *Can. J. Chem.*, 1962, **40**, 2267) for the equilibrium constant for keto–enol tautomerism.

Table 2 Bimolecular rate constants k for the reactions of carbanions with nitrosating agents

Number	Carbanion from	pK_{ap}	Electrophile	$k/dm^3\ mol^{-1}\ s^{-1}$
	(*a*) Carbonyl compounds			
1	Meldrum's acid	4.83[a]	Cl_2CHCH_2ONO	7.17×10^{-3}[b]
2	Dimedone	5.20[c]	MNTS	2.92×10^{-4}[b]
3	1,1,1-Trifluoropentane-2,4-dione	6.70[d]	MNTS	ca. 2×10^{-5}[b]
4	Indan-1,3-dione	7.40[e]	Cl_2CHCH_2ONO	1.45[b]
5	Pentane-2,4-dione	9.08[f]	MNTS	2.48×10^{-2}[g]
			$EtOCH_2CH_2ONO$	5.76×10^{-3}[b]
			$BrCH_2CH_2ONO$	0.143[b]
			$ClCH_2CH_2ONO$	0.108[b]
			Cl_2CHCH_2ONO	7.6[b]
6	3-Methylpentane-2,4-dione	11.0[h]	MNTS	0.40[b]
			$EtOCH_2CH_2ONO$	0.70[b]
7	Diethyl malonate	13.3[h]	Cl_2CHCH_2ONO	794[i]
	(*b*) Nitro compounds			
8	Nitroethane	8.60[h]	MNTS	2.60×10^{-3}[j]
9	1-Nitropropane	8.98[k]	MNTS	3.65×10^{-3}[j]
			$EtOCH_2CH_2ONO$	2.74×10^{-3}[j]
			$BrCH_2CH_2ONO$	3.71×10^{-2}[j]
			$ClCH_2CH_2ONO$	3.12×10^{-2}[j]
			Cl_2CHCH_2ONO	1.22[j]

[a] Ref. 5. [b] 10% dioxane. [c] Ref. 3. [d] Ref. 27. [e] Obtained by pH measurements of a half-neutralized diketone solution. [f] See footnote on page 1235. [g] 20% dioxane. [h] Ref. 28. [i] 5% dioxane. [j] 15% dioxane. [k] G. W. Wheland and J. Farr, *J. Am. Chem. Soc.*, 1943, **65**, 1433.

Table 3 Influence of the dioxane content of the medium on the first-order pseudoconstant k_0 for the reaction between pentane-2,4-dione (50% in enolate form) and 2-ethoxyethyl nitrite; [pentane-2,4-dione$_{tot}$] = 0.8 mol dm^{-3}

% Dioxane	k_0/s^{-1}
5	2.66×10^{-3}
10	2.47×10^{-3}
15	2.05×10^{-3}
20	1.61×10^{-3}

differing considerably from unity that would explain the observed kinetic isotope effect.

Experiments to determine the effect of the dioxane content of the medium on the reaction rate showed that varying dioxane content from 5% to 20% altered the value of k by only a factor of 1.65 (Table 3).

(b) *Indan-*1,3*-dione and Meldrum's acid.* Plotting k_0 against [enolate] for the reactions of indan-1,3-dione and Meldrum's acid with 2,2-dichloroethyl nitrite in carbonate/bicarbonate buffers, in which the diketones exist as enolates, produced straight lines with appreciable intercepts at the origin (Fig. 2), in accordance with eqn. (3). The bimolecular rate constants obtained from the slopes of these plots are listed in Table 2. The assumption that the non-zero intercepts were due to hydrolysis of the highly reactive 2,2-dichloroethyl nitrite,[22] a process that is also of order one with respect to the alkyl nitrite (the deficient reagent), was supported by independent determination of the extent of this hydrolysis reaction in identical buffers. The intercept at the origin is particularly relevant for the reaction with Meldrum's acid because of both the high buffer concentration used and the low reactivity of the enolate.

$$k_0 = k_{hyd} + k[\text{enolate}] \qquad (3)$$

(c) 3*-Methylpentane-*2,4*-dione.* The bimolecular constants obtained for the reactions of 3-methylpentane-2,4-dione with MNTS and 2-ethoxyethyl nitrite (the only ones it was possible to study) are listed in Table 2.

(d) *Dimedone and* 1,1,1*-trifluoropentane-*2,4*-dione.* In spite of the complex absorbance–time records due to the unstable nature of the oximate formed initially, it was possible to follow the reaction of MNTS with dimedone by HPLC monitoring of MNTS concentration. The fact that the concentration–time data (Table 4) were well fitted by a first-order integrated equation for over five reaction half-lives shows that the reaction between MNTS and the enolate was itself uncomplicated, in spite of the complications arising later. The value so obtained for the bimolecular rate constant in these experiments is listed in Table 2.

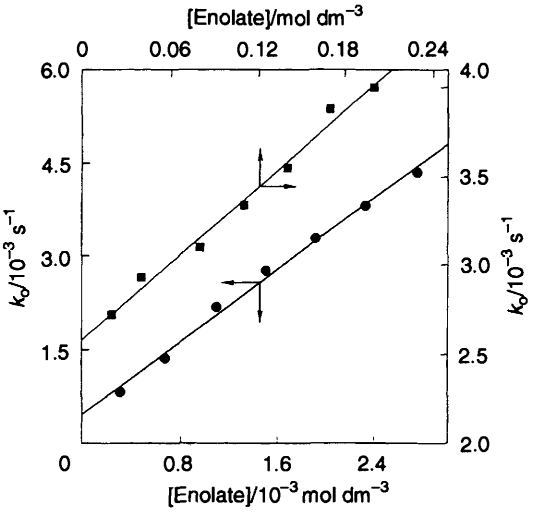


Fig. 2 Influence of the enolate concentration upon the first-order pseudoconstant k_0 for reaction of: (●) indan-1,3-dione with 2,2-dichloroethyl nitrite; pH = 9.91 (carbonate/bicarbonate buffer 1.67×10^{-2} mol dm^{-3}); 10% dioxane; T = 25 °C; (■) Meldrum's acid with 2,2-dichloroethyl nitrite; pH = 9.71 (carbonate/bircarbonate buffer 0.5 mol dm^{-3}); 10% dioxane; T = 25 °C

The reaction of MNTS with the enolate from 1,1,1-trifluoropentane-2,4-dione was extremely slow; after 14 h, the changes in the spectra of reaction mixtures containing 0.425 mol dm^{-3} diketone (95% in enolate form) were slight and probably due to decomposition of the ketone, since the concentration of MNTS was practically unaltered. The estimated bimolecular rate constant listed in Table 2 was calculated from regularly spaced HPLC determinations of [MNTS] in a reaction mixture

Table 4 Typical [MNTS]–time data for the reaction of MNTS with 0.133 mol dm^{-3} dimedone at pH = 6.2 in 10% dioxane

[MNTS]/mol dm^{-3}	t/s
2.23×10^{-4}	2.65×10^{2}
2.01×10^{4}	4.54×10^{3}
1.57×10^{-4}	1.25×10^{4}
1.23×10^{-4}	1.98×10^{4}
8.90×10^{-5}	2.94×10^{4}
6.29×10^{-5}	3.82×10^{4}
1.24×10^{-5}	8.38×10^{4}
8.72×10^{-6}	9.60×10^{4}

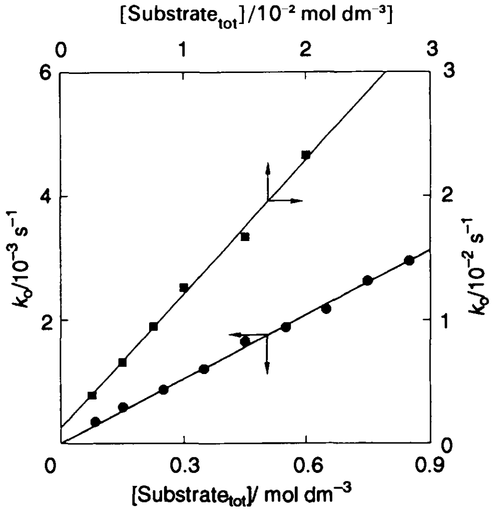


Fig. 3 Influence of the total substrate concentration upon the first-order pseudoconstant k_0 for reaction of: (●) 1-nitropropane with MNTS; pH = 10.3; 15% dioxane; T = 25 °C; (■) 1-nitropropane with 2,2-dichloroethyl nitrite; pH = 9.91 (carbonate/bicarbonate buffer 0.1 mol dm^{-3}); 15% dioxane; T = 25 °C

initially containing 3.58×10^{-2} mol dm^{-3} diketone at pH 7.06 (maintained by the ketone itself, whose pK_a is 6.7[27]); after 16 h, MNTS concentration had only fallen by 3.6%, implying an upper limit of 2.19×10^{-5} dm^3 mol^{-1} s^{-1} for the bimolecular constant. The reactions of this substrate with the alkyl nitrites used were always much slower than the hydrolysis of the latter.

(e) *Diethyl malonate.* The plot of k_0 against substrate concentration for the reaction between diethyl malonate and 2,2-dichloroethyl nitrite to yield diethyl oximinomalonate[1] in carbonate/bicarbonate buffers of pH 9.7 had a small but significant intercept at the origin whose value, $(2.2 \pm 0.3) \times 10^{-3}$ s^{-1}, agrees well with the value determined independently for the first-order pseudoconstant governing the hydrolysis of the alkyl nitrite in the same buffer, 2.0×10^{-3} s^{-1}. The value of 794 dm^3 mol^{-1} s^{-1} obtained for the bimolecular rate constant is based on a value of 13.3[28] for the pK_a of diethyl malonate.

Nitrosation of Nitro Compounds.—The bimolecular constants obtained for the nitrosation of the two nitro compounds studied, nitroethane and 1-nitropropane, are listed in Table 2. Fig 3 shows two examples of the k_0–[substrate] plots from which they were calculated. Again, the small intercept at the origin in Fig. 3 for the reaction of 1-nitropropane with 2,2-dichloroethyl nitrite in carbonate buffer, is quantitatively in keeping with the rate of hydrolysis of the alkyl nitrite in the buffer used.

Attempts to study the nitrosation of other nitro compounds were frustrated by the instability of the latter.

Discussion

Table 2 lists all the bimolecular rate constants for the studied reactions between electrophiles and carbanions, together with values of pK_{ap} (K_{ap} = [carbanion][H$^+$]/[neutral substrate]) obtained either from the literature or in this work (by measuring the pH of substrate solutions partially neutralized with NaOH). Analysis of the results obtained with the enolate of pentane-2,4-dione and alkyl nitrites shows considerable acceleration of the reaction when the nitrosating agent bears electron-withdrawing substituents; the slope of the corresponding Taft plot† is 4.8 (Fig. 4). This finding would appear to be in keeping with the oxygen atom acquiring appreciable negative charge in the transition state (*i.e.* considerable alkoxide character), as was assumed above in discussing the solvent isotope effect of 1.7 for nitrosation by 2-ethoxyethyl nitrite (Scheme 1). MNTS is slightly more efficient than 2-ethoxyethyl nitrite in transferring the NO group to the enolate; both electrophiles are also known to react with nucleophilic nitrogen compounds at similar rates.[19b] The same pattern of behaviour is exhibited by the nitrosation reactions of the anion of 1-nitropropane, though in this case the Taft plot has a smaller slope (3.8) and lies at smaller k values than the plot for the enolate of pentane-2,4-dione (*i.e.* the enolate is both more reactive and more selective than the nitronate ion, which constitutes another counter example[29] to the reactivity–selectivity principle).

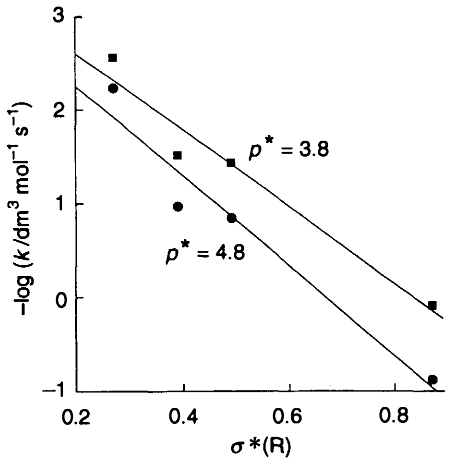


Fig. 4 Taft plot for the reaction of several alkyl nitrites R-O-N=O with: (●) pentane-2,4-dione; 20% dioxane; (■) 1-nitropropane; 15% dioxane

The anions of pentane-2,4-dione and 1-nitropropane both have similar basicity (pK_a *ca.* 9). It is therefore interesting to compare their reactivities as nucleophiles towards the NO group. We observe that the enolate ion is in every case somewhat more reactive than the nitronate ion (between 2 and 10 times). This difference can be considered 'abnormally' low if compared with that found in other chemical processes. In particular, the difference in reaction rates for protonation reactions is much higher. H_3O^+, for example, reacts with the nucleophilic carbon atom of the pentane-2,4-dione anion at a rate of 1.67×10^7 dm^3 mol^{-1} s^{-1},[28] whereas the protonation of the nitroethane anion is much slower,[28] 15 dm^3 mol^{-1} s^{-1}. This enormous difference (a factor of 10^6) has been considered as evidence of the high intrinsic barriers hindering the reactions of nitro compounds. Both these rates contrast with the reactivities of 'normal' bases (*i.e.* N- or O-bases), of similar basicity, whose

---

† Values of σ^* were taken from: C. Hansch and A. Leo, *Substituent Constants For Correlation Analysis in Chemistry and Biology*, Wiley-Interscience, John Wiley & Sons, New York, 1979. In the case of the $Cl_2CH\text{-}CH_2\text{-}$ group, for which no σ^* value is available, an estimation was made by using the value corresponding to $Cl_2CH\text{-}$ corrected by a factor of 0.45. This factor—reflecting the attenuating effect of a methylene moiety—was estimated from comparison of σ^* values in the case of several $X_nC\text{-}CH_2\text{-}$ and X_nC-groups.

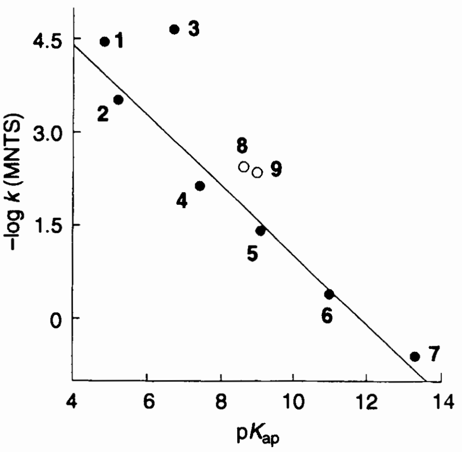


Fig. 5 Brønsted-type plot for the reaction of carbanions with MNTS. Bimolecular rate constants refer to 10% dioxane. Identification of substrates is as defined in Table 2.

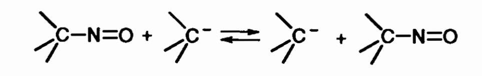
protonation by H_3O^+ is so fast that it is limited by the encounter rate (*ca.* 5 × 10^{10} dm^3 mol^{-1} s^{-1}).[30] However, this pattern, *i.e.* the reaction of carbanions at much slower rates than 'normal' nucleophiles of similar basicities and the strong influence of structural features, is not exhibited by our nitrosation data: the bimolecular rate constant for the nitrosation of *N*-methylpiperazine (pK_a 9) by MNTS is 7.8 × 10^{-3} dm^3 mol^{-1} s^{-1},[19a] in between the values obtained for the anion of pentane-2,4-dione and 1-nitropropane in this work, which themselves only differ by a factor of about 7. The nitrosation behaviour of carbanions thus appears to be unexceptional, involving reaction rates similar to those of 'normal' nucleophiles and exhibiting little of the structural dependence whose observation mainly in protonation reactions has given rise to much discussion. In this context, it is worth mentioning the good Brønsted plots found by Bordwell and co-workers[31] when studying the reactivity of several families of carbanions and other nucleophiles towards benzyl halides in DMSO.

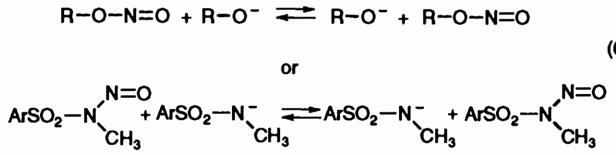
The above conclusion is further supported by Fig. 5, in which the measured or estimated* reactivities of the studied carbanions with MNTS (log *k*) are plotted against their pK_{ap} values, which characterize their dissociation independently of the nature of the acid form, *i.e.*, in the case of the carbonyl compounds, regardless of whether the acid form is the ketone or the enol (in actual fact, the ketone form predominates in all the carbonyl compounds studied except dimedone.)[32] It is generally held that in water the basicities of carbanions are a poor guide to their reactivities when structurally diverse compounds are considered. Fig. 5, however, shows excellent linearity over eight p*K* units for five enolates and the diethyl malonate anion, (β = 0.56 ± 0.04), with the nitro compounds only slightly less reactive than their carbonyl analogues and the enolate of 1,1,1-trifluoroacetylacetone as the only serious deviant.

An explanation for the above behaviour may be sought on the basis of Marcus' theory[33] relating the kinetic barrier $\Delta G^{\ddagger}$ to the thermodynamic barrier ΔG^0 in terms of the intrinsic barrier $\Delta G^{0,\ddagger}$, defined conceptually as the kinetic barrier of a process of the same kind with no thermodynamic barrier [eqn. (4)]. This

$$\Delta G^{\ddagger} = \Delta G^{0,\ddagger}\left(1 + \frac{\Delta G^0}{4\,\Delta G^{0,\ddagger}}\right)^2 \qquad (4)$$

theory was initially developed for electron transfer processes, but has since been applied to proton transfer,[34] methyl transfer[35] and other reactions.[36,37] According to Marcus, the intrinsic barrier determines the kinetic characteristics of a process, so that fast or slow, normal or abnormal processes will differ in the magnitude of their intrinsic barriers. Values of ΔG^0 for our reactions are not known and therefore separation of the contributions due to thermodynamic barriers and intrinsic barriers to the overall rate constants is not possible for our reaction, *i.e.* knowledge of intrinsic barriers is impossible. However, the fact that enolates, nitronates and amines of similar basicity show similar reactivity irrespective of their structural differences seems to suggest that big differences in overall intrinsic barriers are not taking place in our case. Marcus theory can help to understand qualitatively this possibility. For our NO transfer process the intrinsic barrier corresponds to the mean of the kinetic barriers of the two identity transfer processes involving the donor [eqn. (5)] and the acceptor [eqn. (6)].


(5)



$$R{-}O{-}N{=}O + R{-}O^- \rightleftharpoons R{-}O^- + R{-}O{-}N{=}O$$

or

$$ArSO_2{-}N(N{=}O)(CH_3) + ArSO_2{-}N^-(CH_3) \rightleftharpoons ArSO_2{-}N^-(CH_3) + ArSO_2{-}N(N{=}O)(CH_3)$$

(6)

Marcus[38,39] has suggested that the fact that the correlation of log *k*–p*K* data for the deprotonation of series of nitro compounds by a single 'normal' base (or for the reactions of series of carbanions with a single normal acid) yields Brønsted exponents outside the usual range (0–1), while unexceptional exponents are obtained when a single C-acid or carbanion is reacted with a series of normal bases or acids, may be interpreted as reflecting a significant difference in magnitude between the identity intrinsic barriers. If the barrier to the identity transfer involving C-acid and carbanion is much greater than that of the corresponding process for the normal base and acid (which is in fact known to be small), any variations in the former associated with the nature and the structure of the particular C-acid or carbanion will be passed on almost entirely to the intrinsic barrier of the overall reaction [eqn. (5)].

Turning to our situation, the question arises as to which is the magnitude of our intrinsic barriers. The identity transfer of the NO group from a *C*-nitroso compound to the conjugate carbanion will probably have a high intrinsic barrier (since it may reasonably be supposed to be higher than that involved in the corresponding proton transfer). This barrier will be influenced by all changes taking place along the reaction: bond making and breaking, solvent and electronic reorganization. With respect to the intrinsic barrier of the identity NO transfer in eqn. (6), an estimation in the case of 2-ethoxyethyl nitrite can be made on the basis of the known[40] value of 4.1 × 10^{-3} dm^3 mol^{-1} s^{-1} for the rate constant of reaction (7), $CF_3CH_2O^-$ being

$$EtOCH_2CH_2ONO + CF_3CH_2O^- \longrightarrow EtOCH_2CH_2O^- + CF_3CH_2ONO \qquad (7)$$

---

* The reactivities in Fig. 5 refer to reaction in 10% dioxane solutions; experimental values obtained in the presence of other concentrations of dioxane were corrected (never by more than a factor of 1.3 in *k*) assuming solvent dependence analogous to that observed for the reaction of pentane-2,4-dione with 2-ethoxyethyl nitrite (Table 3). The reactivities of the carbanions whose reaction with MNTS could not be determined experimentally (Meldrum's acid, indan-1,3-dione and diethyl malonate) were estimated assuming that their reactivities *k* with MNTS and 2,2-dichloroethyl nitrite are in the same ratio as in the case of pentane-2,4-dione.

a better leaving group than $EtOCH_2CH_2O^-$, this reaction involves overcoming a thermodynamic barrier. However, if log k–pK_a plots for the alkoxide are assumed to be linear and have unit slope (even though a more likely value would seem to be 0.5–0.6, as found for secondary amines[19] and, in this work, for carbanions), then an approximate rate constant of 4×10^{-1} dm^3 mol^{-1} s^{-1} can be calculated for the identity transfer reaction. If the work terms in Marcus' equation are ignored, this value corresponds to a high intrinsic barrier of 75 kJ mol^{-1}, which is of the same order of magnitude as found for the 'slow' proton transfer from nitro compounds to normal bases.

If the 'anomalous' behaviour of pseudoacids with normal bases is a consequence of the strong energetic imbalance between the identity processes contributing to the overall reaction, the absence of such an imbalance between the contributions due to acceptor and donor in our reactions could help to explain the observed non-anomalous behaviour. In fact, the nitrosation of carbanions by normal nitrosating agents will become progressively less sensitive to the nature and structure of the carbanion as the intrinsic barrier for the second process [eqn. (6)] increases. A key point in this discussion therefore concerns the origin of the high intrinsic barriers for NO transfer between N or O nucleophiles, in particular between alkoxides. The O^1–N bond in alkyl nitrites $R–O^1–N{=}O^2$ has considerable double bond character, as is shown, for example by the detection of *cis–trans* isomerism at room temperature.[41] This double bond character will increase the difficulty usually associated with the breaking of bonds between heavy atoms. These 'chemical' factors, together with the solvent reorganization process inherent to the solvation of the leaving RO^- group, will result in quite large intrinsic barriers. The higher the intrinsic barrier for this common process, the less sensitive the overall process to the particular nature of the nucleophile (enolate ion, nitronate ion, amine).

The distinction between bonding and non-bonding contributions to intrinsic barriers can help to explore further the root cause of our satisfactory correlations. The possibility of changes in the intrinsic barrier of the process upon changing the nature of the nucleophile will be further reduced if the dominant contribution to the barrier in eqn. (5) is a 'chemical' component, *i.e.* bond formation and cleavage, with electronic and solvent reorganization changes making only a minor energetic modification in the barrier height. In other words, if the irregular behaviour observed in protonation reactions is, as seems likely, largely due to differences between different carbanions as regards charge rearrangement and solvation, which must be much more dependent than the bonding contribution on the nature and structure of the carbanion, then the irregularity will be greatly reduced if the relative weight of the bonding contribution to the overall barrier is much larger for NO transfer than for the chemically easier proton transfer. The fact that the observed nitrosation reactivities of enolates are similar to those of secondary amines of similar basicity appears to support the notion that the major component of the intrinsic barrier to carbanion nitrosation is the chemical contribution due to the making and breaking of bonds. In other words, we are suggesting large chemical barriers for NO transfer between all kinds of nucleophiles (carbanions, amines, alkoxides, . . .).

According to our ideas, 'fast' reactions of carbanions are more susceptible to anomalies than slow ones, because of the higher influence of the 'anomalous process' (solvation and electronic reorganization) upon the overall process. This is in keeping with the higher sensitivity to the nature of the C-acid/carbanion in proton transfer reactions than in slower processes such as the formation of σ-adducts between carbanions and aromatic rings[42] or the generation of carbanions from alkenes by nucleophilic attack.[43]

However, remains of the nitro compounds anomalies in most reactions can also be detected in our case in the form of the slightly lower reactivity of the nitronate ions with respect to the enolate ions, suggesting that the bonding of the NO group to nitronates is inherently somewhat slower than its bonding to enolates. Arguments of the same kind may explain the violation of the reactivity–selectivity principle noted above (Fig. 4). If the donor contribution to the intrinsic barrier to nitrosation [eqn. (6)] varies slightly from one alkyl nitrite $R–O^1–N{=}O^2$ to another (perhaps largely because of differences in the degree of double bond character of the O^1–N bond, which must depend on the substituents on R), then such changes will be more important, the greater is the ratio between processes (6) and (5). If, as we have just suggested, the contribution of process (6) to the overall process is larger for enolates than nitronates, then it follows that the selectivity of enolates for alkyl nitrites should be greater than that of nitronates, as well as their reactivity, as is indeed seen in Fig. 4.

An explanation for the abnormal slowness of carbanion proton transfer reactions, and for the lack of correlation between the thermodynamic quantity pK_a and rate constants for structurally diverse carbanions, has recently been put forward in terms of the 'principle of non-perfect synchronization',[14,15,44] according to which lack of synchronization among the processes involved in a chemical reaction can give rise to high intrinsic barriers. In the case of carbanion proton transfer reactions, processes of extensive reorganization of charge and solvation are assumed not to be synchronized with bond breaking or formation, and the lag is taken to be greater for nitro compounds than for ketones. In terms of this principle the regularity of behaviour observed for our reactions could be interpreted as evidence for the absence of asynchrony in NO group transfer. This could tentatively be related to the fact that bond cleavage and formation is inherently more difficult for NO transfer than for proton transfer.

It remains to account for the exceptional behaviour of the 1,1,1-trifluoropentane-2,4-dione anion (TFP), which is some 100 times less reactive than its pK_a would suggest (we assume that the pK_a of this anion is 6.7,[27] a value similar to one we have ourselves obtained by measuring the pH of partially neutralized solutions, rather than the older value, 4.7, which seems to have been due to error[45]). A clue to the possible explanation seems to lie in the correlation found by McMahon and Kebarle[46] between the gas phase and solution phase acidities of ketones. According to this correlation the gas phase acidity of TFP, which is greater than that of dimedone, implies a solution phase pK_a of about 4, which would regularize the position of TFP in Fig. 5. The discrepancy between the measured pK_a of TFP and the value predicted from its gas phase acidity may be due to the asymmetry of the molecule, which reduces stabilization of the enolate by resonance and the consequent stabilization of the oxygen atoms by solvation; these circumstances must reduce the stabilizing effect of charge withdrawal by the three fluorine atoms.

The above considerations suggest that the reactivity of carbanions may be satisfactorily correlated with their gas phase acidity. This notion is further supported by the fact that both the rates of carbanion nitrosation measured in this work and the gas phase acidities of carbon acids[46] correlate with their apparent solution phase acidity constants, regardless of whether the predominant form in solution is the ketone or the enol. It should be noted that the gas phase basicity of carbanions is closely linked to their ionization potential,[46] and that according to Pross and Shaik's[47] state correlation diagram model the kinetic barriers of reactions between electrophiles and nucleophiles must be strongly influenced by the vertical ionization potential of the nucleophile (we have discussed elsewhere[19b] the application of this model to *N*-nitrosation). If the gas phase vertical ionization potentials of diketones exhibit the same order as their vertical ionization potentials in solution, then correlation between gas phase acidities and the reactivities observed in this work means that the latter depend on the ease of electron donation, which will also be correlated with apparent basicity in solution. Thus again we find that it is the intrinsically chemical process—electron transfer between nucleophile and electrophile—that determines the kinetic barrier of these reactions. This notion may have some relation to Nibbering and co-workers'[48] interpretation of the 'ambident' gas phase reactivity of enolates, according to which the reaction path taken by enolates depends on the energy of their HOMO orbitals (and hence on their vertical ionization potentials) rather than on the specific distribution of charge within the enolate.

Acknowledgements

A. R. thanks the *Xunta the Galicia* for a Research Training Grant. Financial support from the *Dirección General de Investigación Científica y Técnica* (project PB90–0767) is gratefully acknowledged.

References

1 O. Touster, *Organic Reactions*, Wiley, New York, 1953; vol. 7, ch. 6.
2 J. R. Leis, M. E. Peña, D. L. H. Williams and S. D. Mawson, *J. Chem. Soc., Perkin Trans. 2*, 1988, 157. J. R. Leis, M. E. Peña and D. L. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 45.
3 P. Roy and D. L. H. Williams, *J. Chem. Res. (S)*, 1988, 122.
4 E. Iglesias and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1989, 343.
5 P. Hervés Beloso, P. Roy and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1991, 17.
6 E. Iglesias and D. L. H. Williams, *J. Chem. Soc., Perkin Trans 2*, 1988, 1035.
7 A. Graham and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1992, 747.
8 A. Graham and D. L. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1991, 407.
9 D. L. H. Williams and L. Xia, *J. Chem. Soc., Chem. Commun.*, 1992, 985.
10 (*a*) F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala and K. C. Yee, *J. Am. Chem. Soc.*, 1969, **91**, 4002; (*b*) F. G. Bordwell, W. J. Boyle, Jr. and K. C. Yee, *J. Am. Chem. Soc.*, 1970, **92**, 5926.
11 F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.*, 1972, **94**, 3907.
12 F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.*, 1975, **97**, 3447.
13 F. G. Bordwell, J. E. Bartmess and J. A. Hautala, *J. Org. Chem.*, 1978, **43**, 3107.
14 C. F. Bernasconi, *Tetrahedron*, 1985, **41**, 3219.
15 C. F. Bernasconi, *Acc. Chem. Res.*, 1987, **20**, 301.
16 A. Pross and S. S. Shaik, *J. Am. Chem. Soc.*, 1982, **104**, 1129.
17 R. A. More O'Ferrall, in *Proton Transfer Reactions*, eds. E. Caldin and V. Gold, Chapman & Hall, London, 1973.
18 N. Agmon, *J. Am. Chem. Soc.*, 1980, **102**, 2164.
19 (*a*) A. Castro, J. R. Leis and M. E. Peña, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1861; (*b*) L. García-Río, E. Iglesias, J. R. Leis, M. E. Peña and A. Ríos, *J. Chem. Soc., Perkin Trans. 2*, 1993, 29.
20 W. A. Noyes, *Org. Synth.*, Coll. Vol. II, 1943, p. 108.
21 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1988.
22 E. Iglesias, L. García-Río, J. R. Leis, M. E. Peña and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1673.
23 J. Lifschitz, *Chem. Ber.*, 1913, **46**, 3233.
24 J. Casado, A. Castro, F. M. Lorenzo and F. Meijide, *Monatsh. Chem.*, 1986, **117**, 335.
25 S. Oae, N. Asai and K. Fujimori, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1124.
26 (*a*) J. Albery, in *Proton Transfer Reactions*, eds. E. Caldin and V. Gold, Chapman & Hall, London, 1973; (*b*) L. Melander and W. H. Saunders, *Reaction Rates of Isotopic Molecules*, J. Wiley, New York, 1980.
27 Y. Komatsu, H. Honda and T. Sekine, *J. Inorg. Nucl. Chem.*, 1976, **38**, 1861.
28 R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 1953, **75**, 2439.
29 P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, 1979, **101**, 3288; P. Dietze and W. P. Jencks, *J. Am. Chem. Soc.*, 1989, **111**, 5880.
30 M. Eigen, *Angew. Chem., Int. Edn. Engl.*, 1964, **3**, 1.
31 F. G. Bordwell and D. L. Hughes, *J. Org. Chem.*, 1983, **48**, 2206; 2216; F. G. Bordwell and D. L. Hughes, *J. Am. Chem. Soc.*, 1984, **106**, 3234.
32 R. P. Bell and G. G. Davis, *J. Chem. Soc.*, 1965, 353.
33 R. A. Marcus, *Annu. Rev. Phys. Chem.*, 1964, **15**, 155.
34 R. A. Marcus, *J. Phys. Chem.*, 1968, **72**, 891; A. O. Cohen and R. A. Marcus, *J. Phys. Chem.*, 1968, **72**, 4249.
35 W. J. Albery, *Annu. Rev. Phys. Chem.*, 1980, **31**, 227; W. J. Albery and M. M. Kreevoy, *Adv. Phys. Org. Chem.*, 1978, **16**, 87.
36 J. Hine, *J. Am. Chem. Soc.*, 1971, **93**, 3701.
37 M. M. Kreevoy and L. S. Hanlee, *J. Am. Chem. Soc.*, 1984, **106**, 2550.
38 R. A. Marcus, *J. Am. Chem. Soc.*, 1969, **91**, 7224.
39 A. J. Kresge, *Chem. Soc. Rev.*, 1973, **2**, 475.
40 J. R. Leis, M. E. Peña and A. Ríos, unpublished work.
41 R. N. Haszeldine and B. J. Mattison, *J. Chem. Soc.*, 1955, 4172.
42 M. R. Crampton and J. A. Stevens, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1715.
43 C. F. Bernasconi, *Tetrahedron*, 1989, **45**, 4017.
44 C. F. Bernasconi, *Acc. Chem. Res.*, 1992, **25**, 9.
45 J. C. Reid and M. Calvin, *J. Am. Chem. Soc.*, 1950, **72**, 2948.
46 T. B. McMahon and P. Kebarle, *J. Am. Chem. Soc.*, 1976, **98**, 3399.
47 S. S. Shaik, *J. Am. Chem. Soc.*, 1981, **103**, 3692; A. Pross and S. S. Shaik, *Acc. Chem. Res.*, 1983, **16**, 363.
48 I. L. Freriks, L. J. de Koning and N. M. M. Nibbering, *J. Am. Chem. Soc.*, 1991, **113**, 9119.

Paper 3/00765K
Received 8*th February* 1993
Accepted 1*st March* 1993