

The nitro anomaly and Brønsted β_{nuc} values in $S_{\text{N}}2$ reactions on chlorine[†]

Linoam Eliad and Shmaryahu Hoz*

Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel 52900

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ABSTRACT: The kinetics of chlorine transfer reactions between *N*-chlorosuccinimide (NCS) and four carbon nucleophiles (the conjugated bases of phenyldinitromethane, Meldrum's acid, phenylmalononitrile and phenylnitromethane) in water were determined. A plot of $\log k$ for the $S_{\text{N}}2$ reactions vs the $\text{p}K_{\text{a}}$ of the first three conjugated acids of the nucleophiles gave a straight line with a slope (β_{nuc}) of 1.8. The data point for the mononitro derivative, phenylnitromethane, deviates negatively from the line by 6.7 log units. This deviation is typical of proton transfer reactions and was recently shown to occur also in $S_{\text{N}}2$ reactions on bromine. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: halophilic reactions; $S_{\text{N}}2$ on chlorine; nitro anomaly

INTRODUCTION

One of the most unique and fascinating features of proton transfer reactions is the nitro anomaly. This phenomenon has three different modes of appearance.^{1–4} The most relevant to our study is the one discovered by Pearson and Dillon in 1953.¹ They reported a linear correlation between the kinetics and the thermodynamics of deprotonation reactions of carbon compounds. However, the reactivity of nitroethane and nitromethane deviated negatively from this linear correlation by several orders of magnitude. The presence of another activating group largely attenuates this anomaly. Thus, dinitromethane, for example, fits the linear correlation well. We have recently shown⁵ that an anomalous behavior similar to the above is found in the bromine transfer reactions between carbon donors and carbon nucleophiles.

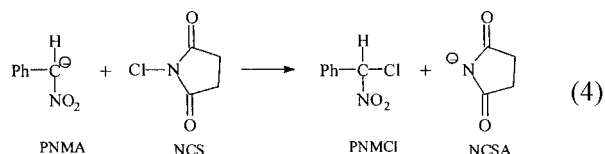
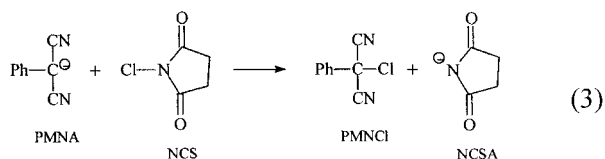
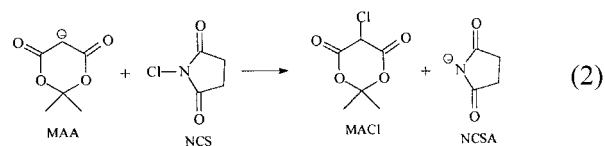
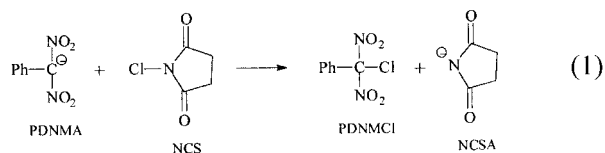
The present study was aimed at exploring the possibility of the existence of the nitro anomaly also in chlorine transfer reactions, in which an *N*-donor (*N*-chlorosuccinimide) is used instead of a carbon donor.

RESULTS AND DISCUSSION

The reactions shown in Eqns (1)–(4) were studied. All the reactions were carried out in buffered aqueous solution.

*Correspondence to: S. Hoz, Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel 52900.
 E-mail: shoz@mail.biu.ac.il

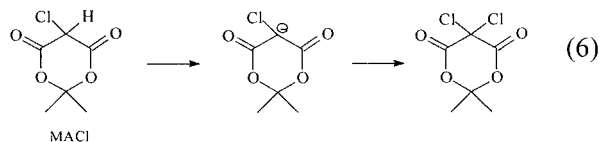
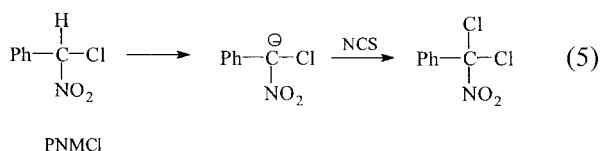
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Successive chlorination

Of the four nucleophiles used in this study, two (PNMA and MAA) are capable of undergoing a second chlorination [Eqns (5) and (6)].

Repetitive scanning in the 200–400 nm range showed that at pH 7.9 PNMA is deprotonated to give the



corresponding anion over 1.5 h (at this pH 96% of the carbon acid is ionized). Addition of 7 equiv. of NCS to the ionized solution resulted in an immediate disappearance of the anion absorption. Addition of 1 equiv. resulted in the disappearance of about half of the absorption. This is interpreted as being due to a rapid deprotonation and a successive chlorination of the monochloro derivative obtained in the first step. The kinetics were studied using up to a 9-fold excess of NCS utilizing a second-order rate equation and taking into account the fact that 2 equiv. of NCS are consumed for each equivalent of PMNA.

The relative reaction rates in the second chlorination process of the Meldrum's acid are entirely different. Whereas PNM undergoes a slow deprotonation and its chloro derivative undergoes a rapid deprotonation (see discussion below on the nitro anomaly), Meldrum's acid and its monochloro derivative are rapidly deprotonated. On the other hand, whereas the chlorination step of the monochloro derivative of PNM is fast, that of the monochloro Meldrum's acid anion is relatively slow. Thus, when a fourfold excess of NCS was added to MAA, the absorption at $\lambda_{\text{max}} = 260$ nm had completely disappeared. However, when the excess of NCS amounted to only 40%, the absorption of MAA vanished and a new peak was observed at $\lambda = 275.5$ nm. Repetitive scanning experiments and single-wavelength monitoring at $\lambda = 260$ and 275.5 nm showed that the monochloro derivative anion is immediately obtained and when a threefold excess of NCS is used; the half-life of MAA is ca 5 s and that of the monochloro derivative is ca 50 s. Therefore, under the reaction conditions (small excess of NCS), the second chlorination step hardly interferes with the determination of the rate constant for the first chlorination step.

Dimerization

When PMNA reacts with PMNCl, a dimer is obtained [Eqn. (7)].

This reaction was previously reported by a few groups⁶⁻⁹ and also observed in our studies of bromine transfer reactions.⁵ Since PMNCl is formed in the reaction of PMNA with NCS, it may react with PMNA

Table 1. Second-order rate constants for the Cl transfer reactions in water at 20 °C

Nucleophile	K (l mol ⁻¹ s ⁻¹)
PDNMA	66
MAA	2.7×10^3
PMNA	3.8×10^5
PNMA	9.7×10^2



and distort the kinetics of the reaction. Therefore, we studied this reaction independently and found it to be first order in each of the components, PMNA and PMNCl, with a rate constant of $(3.5 \pm 2) \times 10^4$ l mol⁻¹ s⁻¹. Thus, this rate constant is much lower than the rate constant of the chlorination of PMNA and therefore will not interfere with the kinetic measurements.

The Brønsted equation

The rate constants for the reactions studied [Eqns (1)–(4)] are given in Table 1. The corresponding Brønsted-type plot is shown in Fig. 1. Three of the points form a straight line with a slope of 1.8 ($r = 0.9933$) but the point for PNMA deviates negatively from the line.

There are essentially two types of linear free energy relationships (LFER) correlating kinetics with thermodynamics. In the first, the kinetics are correlated with the thermodynamics of the same process (as in Brønsted plots¹⁰ for proton transfer reactions). The second is when the rate axis represents a certain reaction, e.g. S_N2 , and the equilibrium axis represents not the thermodynamics of the said reaction but rather that of a model reaction, e.g. proton transfer reaction (the slope in this case is marked β_{nuc} whereas in the former it is β). The first type seems to represent more truly the concept which under-

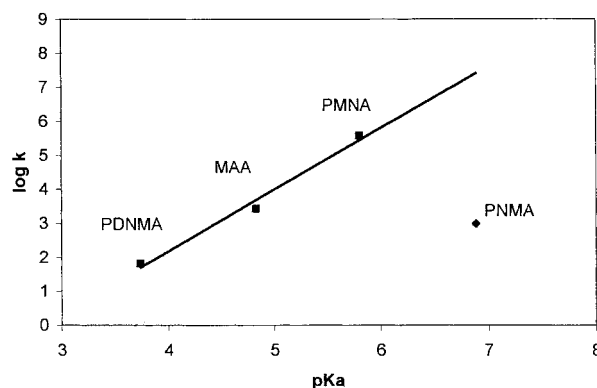


Figure 1. Brønsted-type plot for chlorine transfer reactions from NCS to carbon nucleophiles

Table 2. *Ab initio* calculated energies (B3LYP/6-31 + G*) for the protonated, chlorinated and anionic species in Eqns (8) and (9) and the related reaction energies

Species	<i>E</i> (a.u.)		<i>E</i> (kcal)		
	RH	RCI	R	H <i>trans.</i>	Cl <i>trans.</i>
CH ₃ CN [−]	−132.76169	−592.34378	−132.15665	32.1	55.3
CH ₃ (CN) ₂ [−]	−224.9874	−684.56368	−224.4512	−11.1	8.4
CH ₃ NO ₂ [−]	−245.02479	−704.60902	−244.45022	13.0	37.5
CH ₂ (NO ₂) ₂ [−]	−449.51259	−909.09182	−448.99953	−25.6	−4.3
CH ₃ COCHCOCH ₃ [−]	−345.81191	−805.39867	−345.25361	2.8	28.9
Succinimide	−360.68517	−820.23034	−360.13127		

lines the LFER since β reflects the relative sensitivity of the transition states and ground states to the variation of substituents in the same (and not in model) reaction.

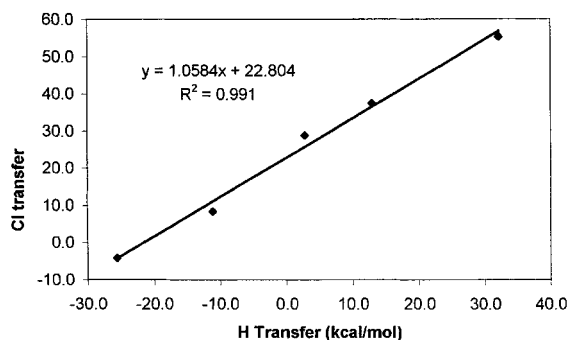
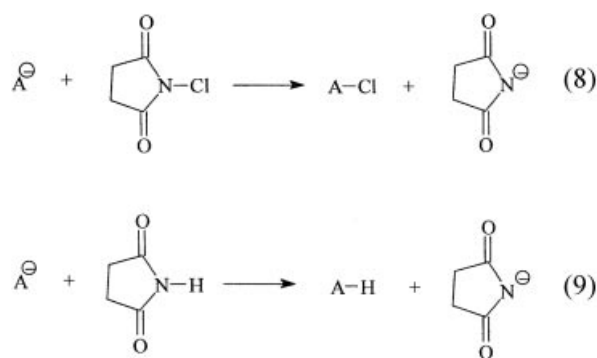
Bordwell and Clemens reported β_{nuc} values close to 1 for electron transfer reactions¹¹ and values in the range 0.3–0.4 for the related nucleophilic (S_N2) reactions by carbon nucleophiles on carbon centers.¹² Since the β_{nuc} value for our reactions is much larger (1.8), we suspected that this might be due to an unexpectedly low sensitivity to substituents in the ground states for proton transfer compared with chlorine transfer. In this case the high ‘kinetic sensitivity’ (1.8) for a chlorine transfer reaction is obtained because the kinetics are compared with the thermodynamics of a model reaction (proton transfer). In

other words, if the thermodynamics of a chlorine transfer reaction are also more sensitive to substituent variation than a proton transfer reaction, a plot of the kinetics vs the thermodynamics of the chlorine transfer reaction itself will give a normal slope (0–1).

In order to explore this possibility, we conducted *ab initio* calculations (Gaussian 98, B3LYP/6-31 + G*)¹³ on the energetics of the equilibria for proton transfer and chlorine transfer reactions shown in Eqns (8) and (9) for a series of model carbon nucleophiles.

The energies obtained for all the species involved are given in Table 2 and the data are presented graphically in Fig. 2. The plot of the reaction energies for chlorine transfer reaction vs those for the proton transfer reaction gives a reasonably linear correlation with $r = 0.9955$ and a slope of 1.06. The slope of nearly unity shows that there are no unusual differential substituent effects in the two series, proton and chlorine transfer reactions. Therefore, assuming that any differential solvent effects, if they exist, are cancelled out, plotting the kinetics of the chlorine transfer reaction vs the pK_a of the corresponding conjugated acids of the nucleophiles is in fact identical with plotting the kinetics of chlorine transfer reaction vs the thermodynamics of the same reaction. Therefore, the slope of the plot in Fig. 1 implies that the sensitivity to substituents of the transition state for the S_N2 reaction on chlorine is nearly double that in the ground state. At the moment we are unable to offer any explanation as to why the geometric/electronic structure of the transition state is so much more sensitive to substituents than the end product.

We will now focus on the deviation from the line of the point for PNMA (Fig. 1). As mentioned in the Introduction, Pearson and Dillon¹ showed that proton transfer reactions involving nitromethane are slower than expected on the basis of their thermodynamic acidity. It is important to point out that this behavior is unique to the case of a single nitro activating group. In cases where there is an additional negative charge stabilizing group the anomaly is largely attenuated. Thus, for example, in the case of two nitro groups on the same carbon, the anomaly is not doubled but rather disappears as the point for dinitromethane is nearly on the line of the Brønsted plot for the other carbon acids.

**Figure 2.** *Ab initio* calculated chlorine transfer vs proton transfer energies

In our case, we studied the reaction of nitromethane with a phenyl group α to the nitro group. However, since relative to the nitro group the acidifying effect of a phenyl group is small, the anomaly is not removed and the point for PMNA deviates negatively from the Brønsted line.

We have not discussed the mechanism of the reaction, which could either be a simple S_N2 reaction or involve an electron transfer process. Clearly the coupling reaction between PMNA and CPMN proceeds through an electron transfer process. However, we have not found any indication for such a coupling process in any of the other reactions we have studied. While we are unable to rule out this possibility, we are more inclined to believe that the Cl transfer in the reactions that we have studied are S_N2 type and display the nitro anomaly rather than to suggest that we have discovered that the nitro anomaly is manifested not only in atom transfer reactions but also in electron transfer reactions.

EXPERIMENTAL

Instrumentation

NMR spectra were recorded on Bruker AC-200, AM-300 and AM-600 spectrometers and measured in $CDCl_3$ solution. Mass spectra were taken with a VG AutoSpec mass spectrometer. UV spectra were recorded on a Kontron 810 UV spectrophotometer. pH was measured using a Radimeter PH52 digital pH meter.

Materials

N-Chlorosuccinimide (NCS) and Meldrum's acid (MA) were purchased from Aldrich. Phenyldinitromethane¹⁴ (PDNM), phenylmalononitrile (PMN)¹⁵ and phenylnitromethane (PNM)¹⁶ were prepared according to published procedures. Although the products chlorophenyldinitromethane (PDNMCl)¹⁷ dichlorophenylnitromethane (dCIPNM)¹⁸ and chlorophenylmalononitrile (CIPMN)¹⁹ are known in the literature, authentic samples were prepared for the purpose of comparison.

Kinetic studies

Methanolic solutions of NCS (25–100 μ l) were injected into a UV cell containing 2.5 ml of the buffered solutions of the nucleophiles. The reactions were first studied by repetitive scanning over the 200–400 nm range in order to identify the appropriate conditions for the kinetic measurements. All the reactions were carried out in buffered aqueous solution (KH_2PO_4 buffer) at $20 \pm 0.3^\circ C$.

The reactions of PMNA with NCS were performed at pH 7.51, monitoring the disappearance of the absorption of PMNA ($\lambda_{max} = 280$ nm). Although very low concentrations of the reactants were used, because of the fast rate of the reaction, we were able to monitor only the second half of the reaction. As a result, the experimental error in the second-order rate constant is $\pm 10\%$. The reaction of PNMA with NCS was performed at pH 8, monitoring the disappearance of the absorption of PNMA ($\lambda_{max} = 293$ nm). The experimental error based on repetitive measurements was 6.5%. The disappearance of the absorption of PDNMA in its reaction with NCS was monitored at $\lambda_{max} = 373$ nm at pH 8.0. The experimental error in this case was $\pm 5\%$. The reactions with MAA were performed at pH 8 using an excess of MA in order to minimize the effect of the consecutive chlorination. The reactions were monitored by following the disappearance of the MAA absorption ($\lambda_{max} = 260$ nm) with an estimated experimental error of 5%.

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