REACTIVITY OF 3-N-(4-CHLORO-3-NITROPHENYL)-SYDNONE IN S_NAR REACTIONS

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Abstract. We have made a kinetic study of the nucleophilic substitution reactions of 3-N-(4-chloro-3-nitrophenyl)sydnone with methoxide ion in methanol:acetone (80:20 v/v) and with piperidine in the same solvent and DMF. These data have been compared with relevant data for the reactions of these nucleophiles with 2-(4-chloro-3-nitrophenyl)-1,3-diphenyl-1,3,4-triazolium-2-thiolate and with 1-chloro-2,4-dinitrobenzene. The special character of a mesoionic system as a substituent in S_NAr reactions, due to the marked separation of positive and negative regions, was clearly evident with the sydnone system. The solvent effects have been analysed.

Introduction

In on going studies (1-4) we have been concerned with the synthesis, reaction mechanisms and biological activity of several mesoionic systems. Many of the studies on mesoionic compounds as such have been concerned with sydnones (1,2,3-oxadiazolium-5-olates), described by Earl and Mackney (5) as early as 1935. Nevertheless, there are very few kinetic studies (1,6,7) of their reactions one being our early study of 3-N-(4-chloro-3-nitrophenyl)sydnone (1).

In the present work we have made a quantitative study of the activating power of the 1,2,3-oxadiazolium-5-olate system linked by its 3-nitrogen to a benzenoid ring subject to aromatic nucleophilic substitution. We have compared this activating power with that of the 1,3,4-triazolium-2-thiolate system similarly linked via its 5-carbon atom (7) and with that of the nitro group virtually a standard reference group, for S_NAr reactions.

Specifically we have determined the rate-coefficients at various temperatures and derived kinetic parameters for the reactions of 3-N-(4-chloro-3-nitrophenyl)-1,2,3-oxadiazolium-5-olate with methoxide ion and with piperidine in methanol: acetone (80:20 v/v) and with piperidine in DMF. The kinetic parameters were in accord with the usual order of nucleophilic strength and solvent effects, while demonstrating again the exceptional character of mesoionic compounds as substrates (8).

Experimental

M.p.s. were determined on a Kofler apparatus and are uncorrected. The infrared spectra were obtained on a Perkin-Elmer spectrometer, model 1420, the NMR ^1H spectra were obtained on a Bruker spectrometer, model AC 200 and the mass spectra were obtained on a Hewlett-Packard spectrometer, model 5987 A. Yields of products were not optimised. N-(4-chloro-3-nitrophenyl)glycine (I) and N,N-(4-chloro-3-nitrophenyl)-nitrosoglycine (II), were prepared according to methods previously described in the literature (1).

N-(4-chloro-3-nitrophenyl)sydnone - The nitrosoglycine (II) (1.97 mmoles) was dissolved in trifluoroacetic anhydride (3.75 ml) at room temperature. After two minutes, yellow crystals separated and were filtered, washed with

ethanol. The product was recrystallized twice from boiling ethanol, to give pale yellow plates. Yield 75.4 %; m.p. 175-176°C (lit.(1), 175-176) (Found: C, 39.72; H, 1.76; N, 17.64 $C_8H_4N_3OCl$ requires C, 39.84; H, 1.67; N, 17.53%); ν_{max}/cm^{-1} 3150 (C-H, aromatic), 1610 (C-O^- mesoionic ring), 1540 and 1350 (NO_2); δH (200 MHz, DMSO-d_6) 7.23 (1 H, s, mesoionic proton), 7.55, 7.45 and 8.05 (3 H, dd, aromatic protons); m/z 241 (M^+).

Kinetic Procedure - Solutions of the mesoionic substrate (0.0125 M) in methanol/acetone 80:20 (v/v) were allowed to react with 1 equiv. of the anionic nucleophile sodium methoxide and 2 equiv. of the neutral of nucleophile piperidine over a range of 30 °C. In the second case the extra equivalent of nucleophilic reagent was required to remove a proton from the initially formed product. From the thermostatted reaction mixture, aliquots (2 ml) were removed at convenient intervals and the reaction stopped with sufficient 0.005 M aqueous HNO_3. The amounts of chloride ion were determined by potentiometric titration against standardised aqueous $AgNO_3$. The rate-coefficients (k_2) were obtained by the usual kinetic analysis, using a linear regression of the points obtained. The potentiometer, coupled to a burette, was a Metrohm-Herisau Dosimatic model.

Table I. Rate coefficients (k_2) for the reactions of 3-N-(4-chloro-3-nitrophenyl)sydnone with piperidine and with sodium methoxide

Nucleophile (solvent)	T (°C)	$k_2 / 10^{-2}$ ($l.mol^{-1}.s.^{-1}$)	Correlation Coefficient
	30.10	0.19	0.9849
	30.10	0.21	0.9949
methoxide	44.75	1.61	0.9951
(MeOH/acetone)*	45.00	1.56	0.9948
	60.00	4.21	0.9992
	61.00	4.20	0.9884
	65.15	0.25	0.9936
	65.15	0.23	0.9973
piperidine	80.10	2.51	0.9889
(MeOH/acetone)*	80.10	2.06	0.9982
	95.50	4.92	0.9459
	95.50	4.39	0.9819
	15.70	0.93	0.9860
	15.70	0.95	0.9930
piperidine	30.55	2.21	0.9957
(DMF)	30.55	2.43	0.9983
	45.00	5.09	0.9943
	45.00	6.00	0.9692

* MeOH/acetone = methanol : acetone 80:20 (v/v)

Table II. Derived kinetic parameters for reactions of 3-N-(4-chloro-3-nitrophenyl)sydnone.

Nucleophile	k_2 (50° C) ($l.mol^{-1}.s^{-1}$)	ln A	$\Delta E^{\neq}$ ($kJ.mol^{-1}$)	$\Delta H^{\neq}$ ($kJ.mol^{-1}$)	$\Delta S^{\neq}$ ($J.mol^{-1} K^{-1}$)	$\Delta G^{\neq}$ ($kJ.mol^{-1}$)	solvent
methoxide	1.87×10^{-2}	27.46	84.47	81.99	-16.61	79.53	MeOH/acetone[a]
piperidine	5.61×10^{-4}	30.26	101.42	98.94	6.67	96.95	MeOH/acetone[a]
piperidine	7.12×10^{-2}	14.51	46.09	43.61	-124.25	80.65	DMF
methanethiolate[b]	5.07×10^{-3}	19.57	67.09	-	-21.80	-	MeOH

[a] acetone 80:20 (v/v)
[b] Ref.1

Table III. Reactions of 2-(-4-chloro-3-nitrophenyl)-1,3-diphenyl-triazolium-5-thiolate with piperidine and with sodium methoxide.

Nucleophile	k_2 (50° C) ($l.mol^{-1}.s^{-1}$)	ln A	$\Delta E^{\neq}$ ($kJ.mol^{-1}$)	$\Delta S^{\neq}$ ($J.mol^{-1}.K^{-1}$)	$\Delta G^{\neq}$ ($kJ.mol^{-1}$)	solvent
methoxide	2.13×10^{-3}	39.95	123.90	78.94	97.85	MeOH
piperidine	5.68×10^{-4}	26.25	90.61	-31.98	98.56	MeOH

Table IV. Reactions of 1-chloro-2,4-dinitro-benzene with sodium methoxide and with piperidine.

Nucleophile	k_2(50° C) ($l.mol^{-1}.s^{-1}$)	ln A	$\Delta E^{\neq}$ ($kJ.mol^{-1}$)	$\Delta S^{\neq}$ ($J.mol^{-1}$)	$\Delta G^{\neq}$ ($kJ.mol^{-1}$)	solvent
methoxide	2.88×10^{-1}	25.91	73.00	-38.50	82.70	MeOH
piperidine	4.85×10^{-2}	15.43	49.58	-	-	MeOH

Results and Discussion

The kinetic data in Tables I and II and our earlier data (8,9) shown in Table III and IV permit an evaluation of the behaviour of mesoionic systems as substituents in S_NAr reactions.

The methoxy-dechlorination of 3-N-(4-chloro-3-nitrophenyl)-sydnone (in MeOH: acetone 80:20 v/v) was compared with that of 1-chloro-2,4-dinitrobenzene (in MeOH). There is some difference in solvent but we consider that there is value in comparing the kinetic data.

With this proviso in mind we showed that 2,4-dinitro-substrate is some 15 times more reactive than the mesoionic substrate. This involves both the intrinsic difference in reactivity and that due to the difference in solvent. It relates to Arrhenius parameters differences (mesoionic substrate - dinitro substrate): $\Delta\Delta E^{\neq}$=11.5 $kJ.mol^{-1}$; Δln A=1.55 (A in $l.mol^{-1} s^{-1}$); $\Delta\Delta S^{\neq}$=1.9 $J.mol^{-1}.K^{-1}$. These differences are coherent with those we have verified and discussed in our kinetic study of *inter alia* methoxy-dechlorination of 5-(4-chioro-3-nitroplenyl)-1,3,4-triazolium-2-thiolate (8).

We consider that the mesoionic substrates, though neutral overall, behave, with respect to solvation, as a pair of ions: thus together with the nucleophile (MeO^-) equivalent to total of three ions. In the transition-state, similar to the σ-complex, the negative charge of the methoxide ion effectively annuls the charge of positive region of the mesoionic substrate, leaving the negatively charged enolate moiety.

As a result there is an unfavourable contribution to $\Delta E^{\neq}$ counterbalanced by favourable contribution to $\Delta S^{\neq}$, due to liberation of bound solvent molecules.

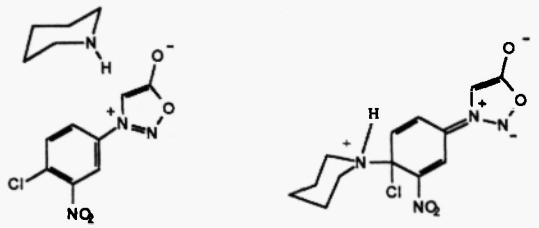
In our early work (1) involving methylthio-dechlorination reactions we estimated a σ^- value for the 1,2,3-oxadiazolium-5-olate system linked by the 3-nitrogen to an eletrophilic benzene ring = 0.71 at 50 °C. More recently (7) we carried out a study of the 1,3,4-triazolium-2-thiolate system linked by its 5-carbon to an electrophilic benzene ring involving methoxy-dechlorination (in MeOH). We compared our data with those for 1-chloro-2,4-dinitrobenzene and thus estimated the σ value for the mesoionic system as 0.72. This is a noteworthy coincidence of values indicating the consistent behaviour of mesoionic systems in reactivity studies.

The methoxy-dechlorination of the 1,2,3-oxadiazolium-5-olate system determined in the present work showed at to be 8.8 times faster than in the 1,3,4-triazolium-2-thiolate system reflecting the lesser polarity of the solvent (80:20 v/v, MeOH:acetone) see Tables II and III. In such a solvent the relatively small anionic nucleophile is less solvated than in pure methanol. This enhances its reactivity via a decrease in the value of $\Delta E^{\neq}$ and a less negative or more positive value of $\Delta S^{\neq}$ (see Tables I and III).

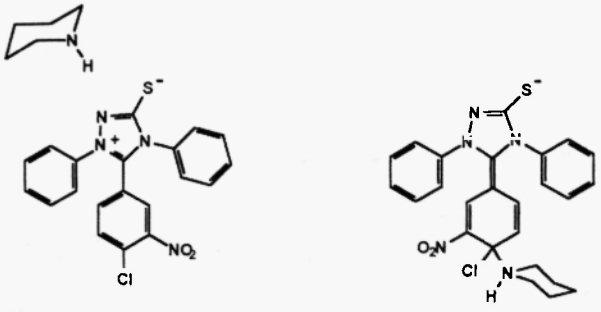
For a discussion of results with the neutral nucleophile piperidine, the rate-coefficients at 50°C are also available with 1-chloro-2,4-dinitrobenzene (9,10). The rate-coefficient ratio dinitro-substrate:mesoionic compound is 86.5. The activation parameters indicate the abnormal behaviour of the mesoionic substrate, with $\Delta E^{\neq}$ = 101,42 $kJ.mol^{-1}$ and lnA = 30.26 compared with $\Delta E^{\neq}$ = 49.58 $kJ.mol^{-1}$, lnA = 15.43 for the dinitro-substrate.

Comparing the reactions of the 1,2,3-oxadiazolium-5-olate and 1,3,4-triazolium-2-thiolate system in piperidine we observed similar reactivity with $k_2 = 5.68.10^{-4}$ and $5.61.10^{-4}$ $l.mol^{-1}.s^{-1}$, respectively. While the rate-coefficients were similar, the Arrhenius parameters indicated different entropic and enthalpic contributions (see Tables II and III). Figure 1 shows a noteworthy difference in charge distribution in the two systems even though both intermediates are neutral overall. This leads to the differences in reactivity in the two solvents, one of which is significantly less polar.

We also compared the reactions of piperidine with the sydnone substrate in MeOH:acetone and in the polar aprotic solvent DMF. This showed very different results (Table I). It is well known that polar aprotic solvents such as DMF solvate anions (except very large ions) much less than the protic or mixed protic solvents. On the other hand polar aprotic solvents solvate cations better (11,12). In our reactions the positive charge becomes more localized in the intermediates (transition states and σ-complex) this causes a decrease in $\Delta E^{\neq}$ which is partly counterbalanced by a more negative $\Delta S^{\neq}$ were DMF used. Specifically the reaction in DMF at 25 °C is 713 times faster than that in MeOH:acetone (80:20 v/v), with values of $\Delta E^{\neq}$=101.42 $kJ.mol^{-1}$ in MeOH:acetone and 46.09 $kJ.mol^{-1}$ in DMF and of $\Delta S^{\neq}$ = +6.67 and -124.25 $J.mol^{-1}.K^{-1}$, respectively.



Initial state of **1** σ-complex of **1**



Initial state of **2** σ-complex of **2**

Figure 1. Initial state and σ-complex for the piperidino-dechlorination of 3-N-(4-chloro-3-nitrophenyl)-1,2,3-oxadiazolium-5-olate (**1**) and 2-(4-chloro-3-nitrophenyl)-1,3-diphenyl-1,3,4-triazolium-2-thiolate (**2**).

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