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EFFECTS OF METHANOL SOLVATION ON THE NUCLEOPHILIC REACTIONS OF THIOLATES WITH 2-SUBSTITUTED-2-NITROPROPANES

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Summary : Methanol solvation prevents $S_{RN}1$ substitution in the reaction of $Me_2C(X)NO_2$ with thiolates and favours an alternative redox reaction to yield disulphide and nitronate.

Thiolates have been shown[1,2] to react with 2-substituted-2-nitropropanes in dipolar aprotic solvents to yield α-nitrosulphides by an $S_{RN}1$ mechanism (E1) and/or disulphide by an X-philic[3] mechanism involving attack by thiolate on the α-substituent to yield a sulphenyl intermediate which subsequently gives disulphide (E2). The X-philic[3] reaction is favoured over $S_{RN}1$ by more strongly nucleophilic thiolates and by more easily abstracted α-substituents (i.e. I>Br>Cl)[1,2].

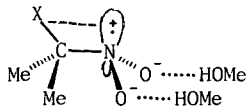
$$Me_2C(X)NO_2 + RS^- \longrightarrow Me_2C(SR)NO_2 + X^- \qquad S_{RN}1 \qquad (E1)$$

$$Me_2C(X)NO_2 + RS^- \longrightarrow Me_2CNO_2^- + RSX \xrightarrow{RS^-} RSSR \qquad X\text{-philic} \qquad (E2)$$

In our studies on the mode of action of the antimicrobial agent, 2-bromo-2-nitropropan-1,3-diol, which owes its activity to the oxidation of protein thiol to disulphide[4], we studied reactions in MeOH and water. We were surprised to find that 2-bromo-2-nitropropan-1,3-diol gave only disulphides when reacted with thiolates; even with weakly nucleophilic thiolates such as *p*-nitrophenylthiolate which gives only $S_{RN}1$ substitution[2] with $Me_2C(Br)NO_2$ in DMF.

We now report (see table) that all the reactions of $Me_2C(X)NO_2$ with thiolates which we studied, which yielded $S_{RN}1$ or mixed $S_{RN}1$/redox products in dipolar aprotic solvents, yielded exclusively redox products (disulphide and nitronate) in MeOH solution. The most pronounced change was the reaction of $Me_2C(Br)NO_2$ with *p*-nitrophenylthiolate which gave 89% of the $S_{RN}1$ product (α-nitrosulphide) in DMF[2] and 51% of disulphide in a faster reaction in MeOH.

Although most of the earlier work[5] in the $S_{RN}1$ mechanism of $R_2C(X)NO_2$ reactions was carried out in EtOH, dipolar aprotic solvents have since been used, and no comment, so far as we are aware, has been made on the effect of protic solvents. $S_{RN}1$ reactions of $R_2C(X)NO_2$ with nitronates proceed faster[5] in DMF or DMSO than in EtOH, but the differences in rate are relatively small. Russell[6] has reported striking differences in reactivity in the $S_{RN}1$ reactions of $Me_2C(X)NO_2$ due to solvation of the nucleophile (protic solvents were not used).

$$[Me_2C(X)NO_2]^{\cdot-}\ solv. \equiv$$  $$\longrightarrow Me_2\dot{C}NO_2 + X^- \qquad (E3)$$

We propose that our results can be explained by strong methanol solvation of the intermediate radical-anion in the $S_{RN}1$ mechanism, which retards the dissociation of $[Me_2C(X)NO_2]^{\cdot-}$ to $Me_2\dot{C}NO_2$ and anion (E3), and hence retards the $S_{RN}1$ chain reaction. The alternative X-philic reaction (E2), however, is not greatly retarded because of the small difference in solvation of thiolates between protic and dipolar aprotic solvents[7,8,9], and therefore predominates and only disulphide is obtained.

Table : $Me_2C(X)NO_2$ + RS^- ⟶ RSSR + $Me_2C(SR)NO_2$

X	R	Conditions[a]	% Yield[b]	
			RSSR	$Me_2C(SR)NO_2$
$(HOCH_2)_2C(Br)NO_2$ Br	*p*-nitrophenyl	MeOH[c], 48h[d], H_2O[c], 24h[d]	98;96	0;0
	p-nitrophenyl	DMF[c], 4h; MeOH:H_2O (85:15), 1h[d]	0;51	89;0
	2-pyridyl	DMF[c], 2h; HMPA[c], 1h; MeOH[c], 21h	5;28;66	10(25)[f];12;0
	p-chlorophenyl	DMF, 2h; MeOH:H_2O (85:15), 5min	70;94	0;0
	p-chlorophenyl	MeOH, 20min	71	0
		+20mol % *p*DNB[c]; +20mol % DTBN[e]	70;68	0;0
$(HOCH_2)_2C(Cl)NO_2$ Cl	*p*-chlorophenyl	H_2O[c], 24h	64	0
	p-chlorophenyl	DMF, 4h	32	35
	p-chlorophenyl	MeOH, 4h	45	0
		+dark, +O_2	32;33	0;0
		+5mol % *p*DNB[e]; +5mol % DTBN[e]	26,28	0;0
	p-chlorophenyl	MeOH, 20min	36(6)[b]	0
		+O_2; +20mol % *p*DNB[e]	21(12)[f];18(22)[f]	0;0
		+20mol % DTBN[e]	30	0
SCN	*p*-nitrophenyl	DMSO, 15min	18(18)[f]	17
		+dark; +O_2	28(38)[f];44(62)[f]	21; trace
		+15mol % *p*DNB[e]; 15mol % DTBN[e]	40(36)[f];30(36)[f]	5; trace
	p-nitrophenyl	MeOH:H_2O (80:20), 20min[d]	39	0
	p-chlorophenyl	DMSO, 20min	35(7)[f]	54
	p-chlorophenyl	MeOH, 20min	60	0
		+dark; +O_2	55;53	0;0
		+20mol % *p*DNB[e]; +20mol % DTBN[e]	55;56	0;0
2-thiopyrimidine	*p*-chlorophenyl	DMF[c], 5h; MeOH[c], 5h	20;47	32;0
2-thio-(N-methyl)-imidazole	*p*-chlorophenyl	DMF[c], 5h; MeOH[c], 5h	23;55	46;0

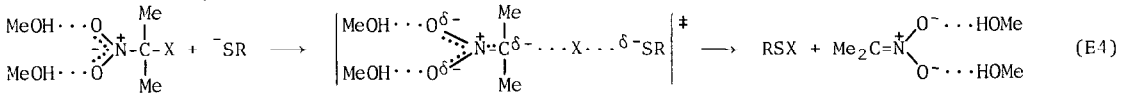
(a) Reactions were carried out under an atmosphere of nitrogen, with light catalysis (2 x 150W Tungsten 'white light' lamps) with a molar ratio of RS^-: $Me_2C(X)NO_2$ of 2:1. (b) % yields are based on RS^-, calculated by ^1H n.m.r. spectroscopy with an internal standard or by isolation. (c) Equi-molar ratio of RS^-: $Me_2C(X)NO_2$. (d) The red colour of *p*-nitrophenylthiolate disappeared within 2min indicating complete reaction. (e) mol % of $Me_2C(X)NO_2$, *p*DNB = *p*-dinitrobenzene, DTBN = di-*t*-butyl nitroxide. (f) Unreacted $Me_2C(X)NO_2$.

The nucleophilic tendency for *p*-nitrophenylthiolate[9] is nearly the same in MeOH as in DMF. Neta[10] has reported that the protonated radical-anion of *p*-nitrobenzylbromide dissociates 60 times slower than the non-protonated radical-anion. Strong H-bonding (protic solvation), of the radical-anion would be expected to exert a similar, albeit smaller, effect on the dissociation of halo-nitro radical-anions. The structures for $[Me_2C(X)NO_2]^{\cdot-}$ and $Me_2\dot{C}NO_2$ have been elucidated by e.s.r. spectroscopy[11].

The X-philic mechanism (E2) for the formation of the RSX intermediate (i.e. S_N2 attack by thiolate on the α-substituent), and hence the disulphide, is supported by the lack of inhibition by radical traps (O_2 and DTBN), strong electron acceptors (O_2 and *p*DNB), and the absence of light. This lack of inhibition of disulphide formation in DMF and DMSO has been previously reported[1], and the lack of significant inhibition in MeOH for the reactions of $Me_2C(Br)NO_2$ and $Me_2C(SCN)NO_2$ with *p*-chlorophenythiolate excludes a radical radical-anion chain mechanism.

The MeOH reactions appeared to proceed faster than those in dipolar aprotic solvent, especially those with *p*-nitrophenythiolate in which the red colour of the anion faded within

minutes. The reactions of $Me_2C(SCN)NO_2$ with *p*-chloro- and *p*-nitrophenylthiolate in MeOH were complete in 20 min, but in DMSO, still had unreacted starting material after 20 min. Even when the $S_{RN}1$ reaction of $Me_2C(SCN)NO_2$ and *p*-nitrophenylthiolate in DMSO was inhibited, the X-philic reaction was not fast enough to consume all the starting material. These results suggest that the redox reaction to disulphide is faster in MeOH than in DMF or DMSO. We suggest that the most likely explanation is that the nitro group of $Me_2C(X)NO_2$ is solvated by MeOH but not by DMF and DMSO, and that this solvation becomes very strong in the S_N2 transition state thereby lowering the energy of the transition state and increasing the rate of reaction (E4).



(E4)

If our explanation is correct, this reaction shows a novel increase in rate for an S_N2 substitution in MeOH over DMF and DMSO. Several factors however militate against this explanation. Firstly, although thiolates are reported to be similarly solvated[7] in protic and dipolar aprotic solvents, the solvation must be taken into account. Using pk_a's as a guide[7] [e.g. *p*-nitrophenylthiol, pk_a 8.4 (MeOH), 6.3 (DMF), 5.6 (DMSO)], higher solvation and therefore lower nucleophilicity would be expected in MeOH relative to DMF and DMSO.

Secondly, several reports[8,12] clearly show that in the deprotonation of 2-nitropropane the nitro-group is not strongly solvated by protic solvents (H_2O) in the transition state. The rate of deprotonation is therefore faster in DMSO than in water which is in sharp contrast to the opposite large difference in pk_a of 2-nitropropane between water (7.6) and DMSO (16.9)[8]. This difference is called the 'nitro anomaly'[8,12]. Even when the solvation of the base is taken into account[13] the rate of deprotonation is faster in DMSO than in water, suggesting by comparison, that abstraction of the α-substituent should be slower in protic solvents than in dipolar aprotic solvents. The differences in reactivity between water and MeOH, and between abstraction of H^+ and α-substituents, may however be counter to the above observations.

Thirdly, $Me_2CNO_2^-$ is reported[14] to be a poor leaving group. Lastly, the more strongly basic the anion the greater the likelihood it will react by a S.E.T. (single electron transfer) mechanism[15] rather than by a S_N2 pathway. Our explanation suggests the opposite, i.e. $S_{RN}1$ (initial S.E.T.) by weakly nucleophilic thiolates, and S_N2 by strongly nucleophilic thiolates.

We therefore suggest that a non-chain mechanism proceeding by initial S.E.T. (E5), closely similar to the $S_{ET}2$ mechanism (E6) proposed by Russell[16] *and Ashby*[17]*, must be considered.*

$$Me_2C(X)NO_2 + RS^- \xrightarrow{S.E.T.} [Me_2C(X)\dot{N}O_2^- \; RS\cdot] \longrightarrow Me_2CNO_2^- + RSX \qquad (E5)$$

$$Me_2C(X)NO_2 + R^- \xrightarrow{S.E.T.} [Me_2C(X)\dot{N}O_2^- \; R\cdot] \longrightarrow [Me_2\dot{C}NO_2 \; X^- \; R\cdot] \longrightarrow Me_2C(R)NO_2 + X^- \qquad (E6)$$

Protic solvation of the intermediate radical-anion would be strong, retarding dissociation to $Me_2\dot{C}NO_2$ and X^- in the $S_{RN}1$ mechanism, but favouring reaction with the thiyl radical to give the sulphenyl intermediate. The observed lack of inhibition or trapping of thiyl radical[1] can be explained by the radical-anion and thiyl being tightly held in a solvent cage. Similarly the initial S.E.T. is rapid, not requiring light catalysis.

$$Me_2C(X)\dot{N}O_2^- \text{ solv.} \longrightarrow Me_2CNO_2^- \text{ solv.} + X\cdot \qquad (E7)$$

$$[RS\cdot \; XCMe_2\dot{N}O_2^-] \longrightarrow [\overset{\delta\cdot}{RS}\cdots X\cdots \overset{\delta\cdot}{C}Me_2NO_2^-]^{\ddagger} \longrightarrow RSX + Me_2CNO_2^- \qquad (E8)$$

$$PhS\cdot + (RONs)^{\cdot-} \longrightarrow PhSR + {}^{-}ONs \qquad (E9)$$

There is no evidence to suggest that protic solvated halo-nitro radical-anions undergo dissociation to nitronate and X·[10,11] (E7). We therefore suggest the reaction in the cage is a S_H2[18] type reaction with a transition state as shown (E8), i.e. this alternative breakdown only takes place in the presence of a reactive free radical (RS·) in the solvent cage. This mechanism can apply to reactions in DMF/DMSO and in MeOH, but would be more favoured in MeOH. This reaction of a thiyl radical with a radical-anion (E9) has been reported[19].

The reaction of $Me_2C(Cl)NO_2$ with *p*-chlorophenylthiolate is slow in MeOH and in DMF. The DMF reaction yields $S_{RN}1$ and redox products but the MeOH reaction yields only disulphide, which is slightly inhibited by O_2, *p*DNB and DTBN. We suggest that this inhibition is explained either by slight inhibition of the non-chain $S_{ET}2$ mechanism expounded above or by a chain oxidative dimerisation mechanism[20] (E11-12) as proposed for the reaction of enolates with $Me_2C(X)NO_2$. Lower reactivity would allow diffusion from the solvent cage (E10) and MeOH solvation would favour a second S.E.T. (E11) rather than dissociation of the radical-anion ($S_{RN}1$ in DMF).

$$[Me_2C(X)\dot{N}O_2^{-}\ RS\cdot] \xrightarrow{\text{diffusion}} RS\cdot + Me_2C(X)\dot{N}O_2^{-} \qquad (E10)$$

$$Me_2C(X)\dot{N}O_2^{-} + RS^{-} \xrightarrow{\text{S.E.T.}} [Me_2CNO_2^{-}\ X^{-}\ RS\cdot] \longrightarrow Me_2CNO_2^{-} + X^{-} + RS\cdot \qquad (E11)$$

$$RS\cdot + RS^{-} \longrightarrow [RSSR]^{\cdot-} \xrightarrow{Me_2C(X)NO_2} RSSR + [Me_2C(X)NO_2]^{\cdot-} \qquad (E12)$$

We conclude that solvation by MeOH has a major effect on the reactions of $Me_2C(X)NO_2$ with thiolates, i.e. retards $S_{RN}1$ substitution, but favours redox by an X-philic or $S_{ET}2$ type mechanism. Further studies to prove the intermediacy or absence of thiyl radicals in these reactions are underway.

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