Rate Acceleration by Steric Inhibition to Solvation of Sulphur Nucleophiles in Acyl Transfer Processes. A Comparison of Steric Effect in Nucleophilic Substitutions at Carbonyl and Aromatic Carbon Atoms

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Summary On increasing the size of the alkyl group in the *ortho*-position of benzenethiol from methyl to t-butyl the nucleophilicity of benzenethiolate is found to increase in carbonyl carbon atom substitution and to decrease in nucleophilic aromatic substitution; steric inhibition to solvation of the anionic sulphur nucleophile is invoked to account for the rate-accelerating steric effect.

STERIC effects in the vicinity of the nucleophile have been widely studied in nucleophilic substitutions at aromatic (C_{Ar}) and carbonyl (C_{CO}) carbon atoms. However in all cases a rate decrease has been observed, usually attributed to an increase of crowding in the transition state.[1]

We have now found that in the reaction of arenethiolates with *p*-nitrophenyl acetate (PNPA), which involves nucleophilic displacement at C_{CO}, and with 2,4-dinitrophenyl acetate (DNPA) and 2,4-dinitrophenyl benzoate (DNPB), which involve concomitant nucleophilic displacement at C_{CO} and C_{Ar}, increasing the size of the alkyl group in the *ortho*-position of benzenethiol from methyl to t-butyl leads to a rate acceleration in the C_{CO} substitution and a rate retardation in the C_{Ar} substitution. The reactivity of the same substrates with *p*-methyl and *p*-t-butyl substituted benzenenethiolates has been also determined and compared with that of unsubstituted and *ortho*-substituted benzenethiolates in order to obtain a significant measure of steric hindrance free from polar effects. The results are in the Table. As expected on the basis of σ-values,[2] the reactivity

TABLE. Rate constants[a] for the reaction of PNPA, DNPA, and DNPB with X-substituted arenethiolates in 95% (v/v) aqueous ethanol at 22 °C.

	PNPA[b]		DNPA[c]				DNPB[c]			
X	$10^2 k_{CO}$	(k_o/k_p)	k_{CO}	$(k_o/k_p)_{CO}$	k_{Ar}	$(k_o/k_p)_{Ar}$	k_{CO}	$(k_o/k_p)_{CO}$	k_{Ar}	$(k_o/k_p)_{Ar}$
H[d]	25·4		31·9		34·2		11·7		62·4	
o-Me	35·6		40·9		57·0		19·3		103·5	
		0·74		0·7		0·56		0·69		0·55
p-Me	48·3		58·8		101·9		28·0		187·3	
o-But^t	125·0		94·5		40·5		39·0		72·6	
		2·9		2·0		0·43		2·1		0·38
p-Bu^t	43·2		46·5		93·2		18·6		190·9	

[a] l mol^{-1} s^{-1}. [b] [PNPA] = 4×10^{-5} M; [ArS$^-$] = 10^{-2} M; $[ArSH]_{free} = 10^{-2}$ M. [c] [DNPA] and [DNPB] = 10^{-5} M; [ArS$^-$] = 2×10^{-4} M; $[ArSH]_{free} = 3 \times 10^{-3}$ M. [d] Values taken from ref. 3.

increases on going from the unsubstituted to the *p*-methyl and *p*-t-butyl substituted benzenethiolate, the effect being more pronounced for C_{Ar} than for C_{CO} substitution, in accordance with the lower ρ-value of the nucleophile for C_{CO} substitution compared with the C_{Ar} substitution.[3] Rate acceleration occurs also with an *o*-methyl group, although the effect is less pronounced than with *p*-methyl. The k_{ortho}/k_{para} values for the Me-group are always less than unity, and somewhat lower for C_{Ar} than for C_{CO} substitution. This indicates a larger steric requirement of the transition state for aromatic as compared to carbonyl carbon atom nucleophilic substitution.

As seen from the Table the effect of an *o*-t-butyl group, compared to *o*-methyl and *p*-t-butyl, is clearly opposite in the two types of substitutions: rate-retarding in C_{Ar} and rate-accelerating in C_{CO} substitution. This result can be interpreted in terms of steric inhibition to solvation of the reactant nucleophile.[4] This effect has its origin in the *o*-t-butyl group which generates in the immediate proximity of the anionic sulphur a microscopic hydrophobic environment, which increases the ground-state energy of the nucleophile when this is dissolved in a protic solvent. In the transition state, owing to the larger dispersion of negative charge, this desolvation effect is less important and therefore the steric inhibition to the solvation effect is rate-accelerating. Obviously, besides this effect, a decelerating effect due to steric crowding in the transition state and an accelerating effect of the electronic nature also operate. The observed nucleophilicity of *o*-t-butylbenzenethiolate therefore depends upon the contribution of these three factors, whose degree changes depending on the type of reaction. The fact that in C_{CO} substitutions k_{ortho}/k_{para} for t-butyl is larger than unity is a direct consequence of the lower steric requirement of the transition state in this type of reaction and thus of the predominance of steric inhibition to solvation of the nucleophile.

These results are important because they supply, for the first time in an acyl transfer model process, experimental proof in support of the supposition that steric inhibition to solvation of a hydrophobic nature can be responsible, together with other factors, for the high reactivity of some SH groups present in the ionized form in internal and hydrophobic regions of some cysteine enzymes involved in acyl-transfer reactions.[5]

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[1] G. Bartoli, F. Ciminale, and P. E. Todesco, *J. Org. Chem.*, 1975, 873 and references therein reported; A. J. Kirby in 'Comprehensive Chemical Kinetics', eds. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1972, vol. 10.
[2] J. Hine in 'Physical Organic Chemistry,' McGraw-Hill, New York, 2nd edn., 1962, p. 87.
[3] G. Guanti, C. Dell'Erba, F. Pero, and G. Cevasco, *J.C.S. Perkin II*, 1978, 422.
[4] D. Semenow-Garwood, *J. Org. Chem.*, 1972, 3797.
[5] P. D. Boyer in 'The Enzymes', eds. P. D. Boyer, H. Lardy, and K. Myrback, Academic Press, New York, 1959, vol. I, p. 511; M. R. Hollaway, A. P. Mathias, and B. R. Rabin, *Biochim. Biophys. Acta*, 1964, **92**, 111.