Relative Nucleophilicity of Thiols and Glutathione Towards Benzene Oxide

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Summary The slope (β) of a Brönsted plot of the microscopic pK_a values of the -SH functions of a series of ionic species *vs.* the logarithm of the second-order rate constants for reaction of each species with benzene oxide is 0·22 indicating an early transition state.

Arene oxides serve as intermediates in drug metabolism and the biosynthesis of tyrosine, and as agents in necrosis and hydrocarbon carcinogenesis. Glutathione is known to react with certain aromatic oxides and, thus, functions as a natural detoxification agent. Inferences have been made that glutathione possesses an enhanced ability (over other thiols) to react with arene oxides.[1]

Benzene oxide (BO) exists in equilibria (instantaneous on the time scale of these studies) with the corresponding oxepin[2] which possesses a spectral transition in H_2O at 320 nm. The disappearance of BO (320 nm, 30°, H_2O, μ = 1·0 with KCl) in the presence of varied concentrations of a series of thiols ($[\mathrm{Thiol}_T]$ = 0·02—0·10 M, [BO] = 10^{-4}—10^{-5}M) at constant pH led to the second order rate constants (equation 1) of the Table. Included in the Table are the microscopic pK_a values of the various thiol species determined under the same conditions of μ and T as the

$$-d[\mathrm{BO}]/dt = k_{\mathrm{RS}^-}[\mathrm{RS}^-][\mathrm{BO}] \qquad (1)$$

kinetic experiments but at 10^{-4}—10^{-5} lower $[\mathrm{RSH}_T]$. From a plot of log k_{RS^-} *vs.* the microscopic pK_a values of the conjugate acids of the reactive thiolate species the Brönsted β is calculated as 0·22 (average deviation of log k_{RS^-} = 0·065). The points for the glutathione species do not deviate from the Brönsted plot establishing that glutathione does not have an enhanced nucleophilicity toward

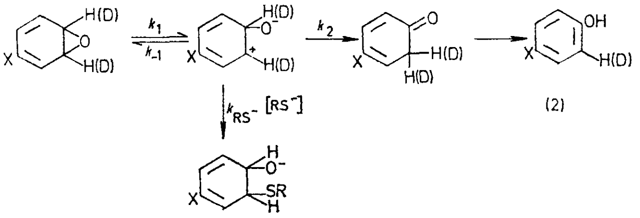
BO but is just that anticipated from the pK_a of its thiol functional group.

Table. Microscopic pK_a values for thiol species and second-order rate constants for reaction of thiolate species with benzene oxide (BO) and Malachite Green carbonium ion (M.G.).

		k_{RS^-}/l mol^{-1} s^{-1}	
RSH species	pK_a	BO	M.G.
HS–CH$_2$CH(NH$_3^+$)CO$_2$Et	7·30	0·055	5 × 10^3
HS–CH$_2$CH(NH$_3^+$)CO$_2^-$	8·21	0·075	4·7 × 10^3
HS–CH$_2$CH$_2$NH$_3^+$	8·22	0·085	7·1 × 10^3
HS–CH$_2$ CO$_2^-$ HCNHCO(CH$_2$)$_2$CHNH$_3^+$ CONHCH$_2$CO$_2^-$	8·72	0·114	
HS–CH$_2$ CO$_2^-$ HCNHCO(CH$_2$)$_2$CHNH$_2$ CONHCH$_2$CO$_2^-$	8·72	0·166[a]	
HS–CH$_2$CH(NH$_2$)CO$_2$Et	8·87	0·144	
(±)-HS–(CH$_2$)$_2$CH(NH$_3^+$)CO$_2^-$	9·02	0·090	
HS–CH$_2$CH$_2$OH	9·45	0·172	
HS–CH$_2$CH(NH$_2$)CO$_2^-$	9·56	0·217	
(±)-HS–(CH$_2$)$_2$CH(NH$_2$)CO$_2^-$	9·69	0·165	
HS–CH$_2$CO$_2^-$	9·82	0·184	1·8 × 10^4

[a] Ionization of the α-amino group (pK_a = 9·46) provides a moderate increase in rate constant.

It has been shown[3] that the spontaneous and A-1 catalysed[4] NIH shift involving BO is characterized by Hammett ρ values of ≈ -7 and that no primary deuterium kinetic-isotope effect is obtained when the migrating hydrogens are replaced by deuterium. This led to the suggestion of the mechanism of equation (2). The value of $\beta = 0·22$ is in accord with an early transition state for the trapping of the zwitterionic intermediate by the highly polarisable thiol anion ($k_{-1} > k_{RS^-}[RS^-] > k_2$). A similarly small sensitivity to base strength is obtained from the k_{RS^-} values for reaction of the most and least basic thiol anions (Table) with the resonance stabilized carbonium ion of Malachite Green.



(2)

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[1] For pertinent references see review by J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, 1972, **28**, 1129.

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