

STRUCTURE-REACTIVITY INDICES FOR THE HYDROLYSIS OF DIOL EPOXIDES OF
POLYCYCLIC AROMATIC HYDROCARBONS

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Summary: Several different computational parameters have been used in an attempt to predict relative reactivity of carcinogenic bay-region diol epoxides. The correlation of experimentally observed hydrolytic reactivity with these parameters is described.

The bay-region theory^{1,2} of carcinogenesis by polycyclic aromatic hydrocarbons predicts that the ultimately carcinogenic metabolites of those hydrocarbons that are biologically active will be benzo-ring diol epoxides in which the epoxide group is located in a bay-region of the hydrocarbon. Tumor studies³ with a number of bay-region diol epoxides and their metabolic precursors have provided strong support for this theory. Significantly, for any one hydrocarbon, the bay-region benzylic position is predicted to be the site at which a carbocation is most easily formed.^{1,2} Since evidence exists for a mechanism involving such a cationic intermediate in the alkylation of nucleic acids by a diol epoxide⁴, the relative ease whereby diol epoxides derived from *different* hydrocarbons can react via a carbocation or related mechanism should be one of the several factors that influence the biological activity of these hydrocarbons and their metabolites. Thus, considerable effort has been directed towards the correlation of the chemical reactivity and biological activity of polycyclic aromatic hydrocarbons and their derivatives with various calculated indices^{1,5-7} related to the ease of formation of a cation at the crucial bay-region benzylic carbon.

It should be possible to corroborate quantitatively the validity of such indices by observations of the chemical reactivity of the diol epoxides in a well defined system. Diol epoxides undergo hydrolysis^{8,9} in aqueous solution according to the rate law, $k_{\text{obsd}} = k_o + k_{\text{H}^+} a_{\text{H}^+}$, to give cis and trans tetraols consistent with a carbocation mechanism.^{9,10} At present we have kinetic data, obtained under identical or closely similar conditions, for the hydrolysis of a series of diol epoxides whose rates of uncatalyzed hydrolysis (k_o) differ by ~3 orders of magnitude. The present report compares the correlation between these hydrolysis rates and four of the more commonly used reactivity indices: $\Delta E_{\text{deloc}}/\beta$, from perturbational molecular orbital calculations¹, $\Delta E_{\pi}/\beta$, from Hückel molecular orbital calculations⁵, $\log(\text{SC ratio})$ from resonance theory^{6,11} and ΔE values (relative to dibenzo[a,i]pyrene) from SCF INDO calculations⁷. We conclude that *there is no substantial difference among the indices examined as predictors of reactivity of bay-region diol epoxides in hydrolysis reactions*. Hence, the use of more sophisticated calculations to derive indices of this type would appear to be of limited value.

Table I lists the four reactivity indices and values of $\log k_{\text{H}}$ (hydronium-ion-catalyzed reaction) and $\log k_o$ for six bay-region diol epoxides. In the Table, isomers 1 and 2 refer to

Table I
Rate constants and reactivity indices for hydrolysis^a of bay-region diol epoxides.

Parent Hydrocarbons	$\Delta E_{\text{deloc}}/\beta^b$	$\Delta E_{\pi}/\beta^c$	Log SC Ratio ^d	ΔE (SCF INDO) ^e	$\log k_o^f$ (1)/(2)	$\log k_{H+}^f$ (1)/(2)
1. Benzo[c]phenanthrene ^g	0.600	0.783	0.532	-	-5.22/-6.10	1.81/2.36
2. Phenanthrene ^h	0.658	0.812	0.523	22	-4.51/-5.07	1.82/2.20
3. Chrysene ^g	0.639	0.803	0.556	19	-4.60/-5.13	1.49/2.05
4. Benz[a]anthracene ⁱ	0.766	0.848	0.602	16	-3.51/-4.55	2.10/2.44
5. Benzo[a]pyrene ^j	0.794	0.867	0.653	2	-2.38/-3.89	2.71/3.15
6. Dibenzo[a,h]pyrene ^k	0.845	0.882	0.718	2	- /-3.5	- /2.93
7. Dibenzo[a,i]pyrene ^k	0.866	0.891	0.726	0	- /-2.92	- /3.30

^aIn 1:9 dioxane-water, ionic strength 0.1 M, 25°C. ^bRef. 1 and D. M. Jerina, J. M. Sayer, H. Yagi, M. Croisy-Delcey, Y. Ittah, D. R. Thakker, A. W. Wood, R. L. Chang, W. Levin, and A. H. Conney, in *Biological Reactive Intermediates II: Chemical Mechanisms and Biological Effects*. R. Snyder, D. V. Parke, J. J. Kocsis, D. J. Jollow, C. G. Gibson, and C. M. Witmer, eds., New York, Plenum Publishing Co., 1982, pp. 501-524. ^cRef. 5. ^dRef. 6. Values not listed in Ref. 6 were calculated by the method described therein. ^eRef. 7. ^fRate constants are in s⁻¹(k_o) or M⁻¹s⁻¹(k_{H+}). For definition of isomers 1 and 2 see text. ^gRef. 13. ^hRate constants in 1:9 dioxane-water were estimated from values in water (Ref. 9) assuming no solvent effect on k_{H+} and a fourfold deceleration of k in the mixed solvent relative to water (cf. Ref. 8). ⁱJ. M. Sayer, H. Yagi, and D. M. Jerina, unpublished data. ^jRef. 8. ^kA. W. Wood, R. L. Chang, W. Levin, D. E. Ryan, P. E. Thomas, R. E. Lehr, S. Kumar, D. J. Sardella, E. Boger, H. Yagi, J. M. Sayer, D. M. Jerina, and A. H. Conney, *Cancer Res.* 41, 2589 (1981).

the diastereomers in which the benzylic hydroxyl groups are cis and trans to the epoxide oxygen, respectively. Plots of log k_o for each set of diastereomers vs. the reactivity indices are shown in Fig. 1. Least squares slopes and intercepts for the analogous plots of log k_H, as well as correlation coefficients (r), are given in Table II. The calculations were performed using the program MLAB¹². The correlations involving log k_o are acceptable in all cases, (r = 0.94 to 0.98) but the best correlations are obtained with the closely related quantities $\Delta E_{\text{deloc}}/\beta$ (PMO) and $\Delta E_{\pi}/\beta$ (HMO). In neutral (k_o) hydrolysis reactions, the isomer-1 diastereomers are somewhat more sensitive than the isomer-2 diastereomers to the ease of cation formation, regardless of which index is chosen. The point for diastereomer 1 of benzo[c]phenanthrene diol epoxide, whose preferred conformation differs from that for other isomer-1 diol epoxides,¹³ shows no significant deviation from the plots vs. $\Delta E_{\pi}/\beta$ or $\Delta E_{\text{deloc}}/\beta$, although the points for both diastereomers of this diol epoxide exhibit negative deviations from the plot vs log (SC ratio). Multiple regression analyses using log k_o (isomer-2) and several combinations of the reactivity indices did not give an appreciably better fit as shown by similar values of the rms error.

The correlations of log k_H with the indices of reactivity (r = 0.85 to 0.97) are generally poorer than those for log k_o. In the case of k_H as well as k_o, there is no large difference in the results with the four indices, although better correlations of log k_H appear to be obtained with the SCF INDO ΔE values. Larger differences between the slopes of the plots for log k_o for a pair of diastereomers vs. any of the indices, compared to the corresponding plots of log k_H, suggest a difference in transition state structure between the two diastereomers that is greater in the k_o than in the k_H reaction.

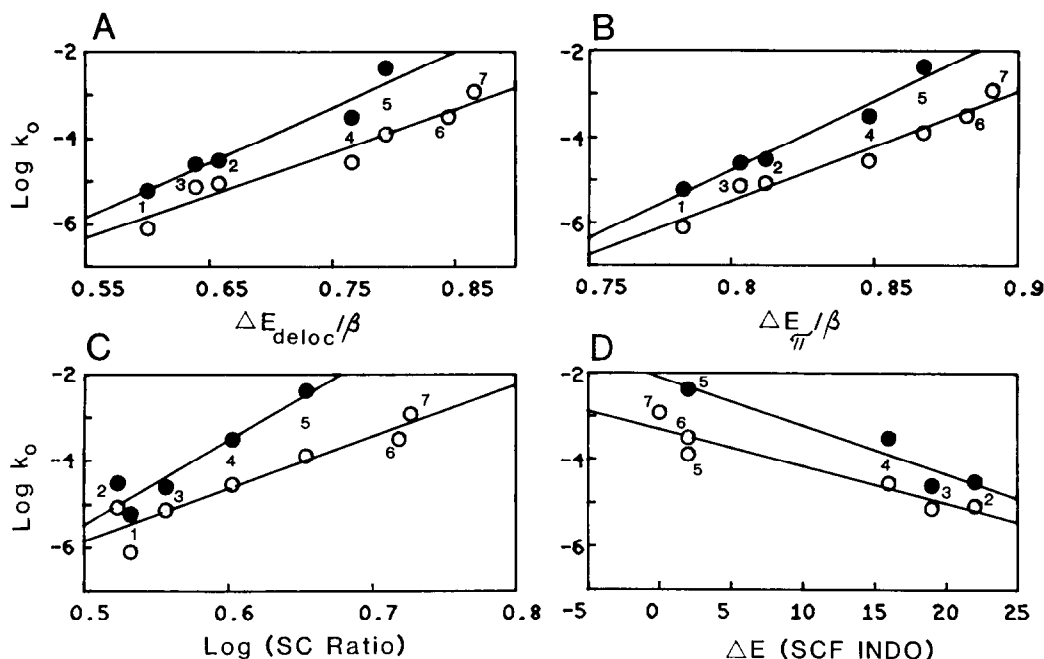


Figure 1. Linear relationships between $\log k_o$ for isomers 1 (●) and 2 (○) of polycyclic aromatic diol epoxides and calculated reactivity indices relating to carbocation formation. The numbers correspond to the compounds listed in Table I. Slopes (m) and correlation coefficients (r) are as follows: A, $k_o(1)$, $m = 12.8$, $r = 0.968$, $k_o(2)$, $m = 10.0$, $r = 0.969$; B, $k_o(1)$, $m = 32$, $r = 0.983$, $k_o(2)$, $m = 25.4$, $r = 0.979$; C, $k_o(1)$, $m = 19.6$, $r = 0.951$, $k_o(2)$, $m = 12.1$, $r = 0.941$; D, $k_o(1)$, $m = -0.112$, $r = 0.954$, $k_o(2)$, $m = -0.085$, $r = 0.949$.

Table II

Slopes and intercepts for linear relationships between $\log k_{H^+}$ and the reactivity indices, with correlation coefficients (r).

Index	Slope (1)/(2)	Intercept (1)/(2)	r (1)/(2)
$\Delta E_{deloc}/\beta$	4.61/4.04	-1.20/-0.35	0.845/0.872
$\Delta E_{\pi}/\beta$	11.43/10.25	-7.41/-5.98	0.852/0.877
Log SC Ratio	7.27/5.16	-2.18/-0.54	0.858/0.895
ΔE (SCF INDO)	-0.053/-0.051	2.81/3.20	0.903/0.966

One goal of these studies is to provide insight into the extent of C-O bond breaking and positive charge development in the transition state for diol epoxide hydrolysis reactions. Relationships such as Fig. 1 provide limited information about the transition state since they cannot easily be compared with structure-reactivity relationships for other reactions. For this purpose, Hammett-type linear free energy relationships are more useful, but few of the relevant σ^+ values¹⁴ are available. We have used a linear relationship between \log (SC ratio) and σ^+ for solvolyses of arylmethyl compounds, previously pointed out by Herndon^{6,11}, to estimate σ^+ values of 0.77 and 0.74 for the 1- and 3-benzo[a]pyrenyl substituents, corresponding to the bay-region cations derived from 1,2,3,4-tetrahydrodibenzo[a,i]- and tetrahydrodibenzo[a,h]-pyrene, respectively. A similar method of estimation using $\Delta E_{\pi}/\beta$ (HMO) gives $\sigma^+ = 0.79$ and

0.74 for these two compounds.¹⁵ A σ^+ value between 0.19 (HMO) and 0.30 (log SC ratio) is estimated for 1,2,3,4-tetrahydrobenzo[c]phenanthrene. The resultant Hammett-type plots of $\log k_o$ vs σ^+ using these values and literature values¹⁴ of σ^+ corresponding to the tetrahydro derivatives of chrysene, phenanthrene and benz[a]anthracene have slopes (ρ^+) of -5.97 ($r = 0.980$) and -4.56 ($r = 0.966$) for isomers 1 and 2, respectively.¹⁶ The point for benzo[a]pyrene diol epoxide 2 shows a severe negative deviation from the plot if the published σ^+ value of -1.0¹⁴ is used. The abnormality of this value of σ^+ has previously been pointed out.^{11,14} Use of $\sigma^+ = -0.65$ estimated by Streitwieser¹⁴ from CNDO calculations gives a good fit of this point to the $\sigma^+ - \rho^+$ plot for isomer 2. Maximal values of ρ^+ for carbocation-forming equilibria¹⁷ and for rates¹⁴ involving transition states with a large degree of carbocation character are ca. -5.5 to -7.5, compared with our values of -4.6 and -6.0. Thus we conclude that there is very substantial, although probably not maximal, development of positive charge in the transition states for neutral hydrolyses of these diol epoxides.

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- (16) The points for the benzo[a]pyrene and benzo[c]phenanthrene derivatives were not included in the calculations for isomer 2. Inclusion of these points (with σ^+ for the benzo[a]pyrene derivative = -0.65) gives a slope of -4.80 and a correlation coefficient of 0.978.
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