Arene Oxide–Oxepin Isomerization. Theoretical Predictions and Experimental Evidence

Derek R. Boyd and Michael E. Stubbs*[1]

Contribution from the Department of Chemistry, The Queen's University of Belfast, Belfast, BT9 5AG Northern Ireland. *Received June 17, 1982*

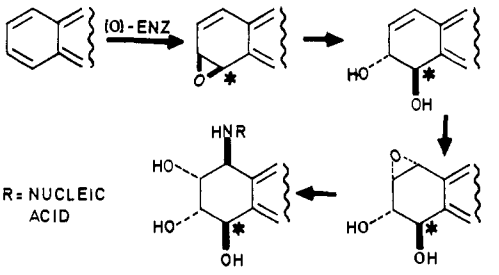
Abstract: The title reaction is probably implicated in the observed spontaneous racemization of certain optically active arene oxides, which have biological significance as metabolites of polycyclic aromatic hydrocarbons. Several simple methods, based on perturbational molecular orbital theory, are presented that facilitate the prediction of electronic energy differences between the isomers. Comparison of the predictions among themselves and with experimental evidence allows the selection of the most reliable methods and the semiquantitative prediction of the position of equilibrium and the rate of isomerization. Results are listed for 75 compounds, and the methods may be used readily for the calculation of any additional examples. The results suggest the classification of polycyclic arene oxides into a number of classes, not mutually exclusive, based on shared structural features.

Following an initial proposal in 1956,[2] the formation of epoxide (arene oxide) intermediates in the metabolism of polycyclic aromatic hydrocarbons (PAHs) by animals was experimentally verified in 1968[3] with the isolation of naphthalene 1,2-oxide (**2**) (Chart I) as a metabolite of naphthalene. Preferential addition of an oxygen atom to one stereoheterotopic face of an aromatic ring by the monooxygenase enzyme is now established, but the feasibility of observing optically active arene oxides as metabolites depended upon the optical stability of the arene oxides, and this was first demonstrated for (**2**) by Boyd et al.[4] through synthesis of **2** in optically active form. The absolute stereochemistry of the benzylic chiral center created during the enzyme-catalyzed epoxidation step is maintained during subsequent metabolic steps, leading ultimately to the formation of a covalent bond between the chiral epoxydiol intermediate and an amino group of a nucleic acid (Scheme I).[5]

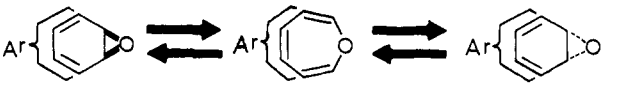
Investigation of the importance of metabolic intermediate chirality for the biological effects (mutagenicity, carcinogenicity, etc.) of PAHs and for the kinetics of the liver microsomal enzymes required synthetic routes to optically active metabolites; such routes, applicable to various classes (bay, non-K and K region) of arene oxide, have been developed in this and collaborating laboratories. By these means, optically pure arene oxides have been prepared in the naphthalene (1,2, (**2**)),[6] anthracene (1,2, (**5**)),[6] benz[*a*]anthracene (5,6, (**19**);[7,8] 8,9, (**20**);[9] 10,11, (**22**)[8]), and benzo[*a*]pyrene (4,5, (**64**);[7] 7,8, (**65**)[5]) series.

When similar methods were employed to prepare certain optically active arene oxides of chrysene (1,2, (**23**);[10] 3,4, (**25**)[11]), these compounds were observed to racemize spontaneously at ambient temperature in a clean first-order process. A similar observation was made in the phenanthrene (1,2, (**8**);[12] 3,4, (**10**)[12,13]) series, where rate measurements were more difficult because of the greater rapidity of racemization, while with two of the benz[*a*]anthracene oxides (1,2, (**16**); 3,4, (**18**))[14] no optical activity was observed, the racemization presumably being fast on the time scale of the experiment. While we are unaware of any data unequivocally implicating such racemizations during in vivo and in vitro enzymic metabolism of PAHs, the possibility of this occurring and having significant stereochemical consequences for the products cannot be excluded. It would be desirable if workers in this field were aware of cases where racemization of the first-formed arene oxide is a possibility.

Scheme I



Scheme II

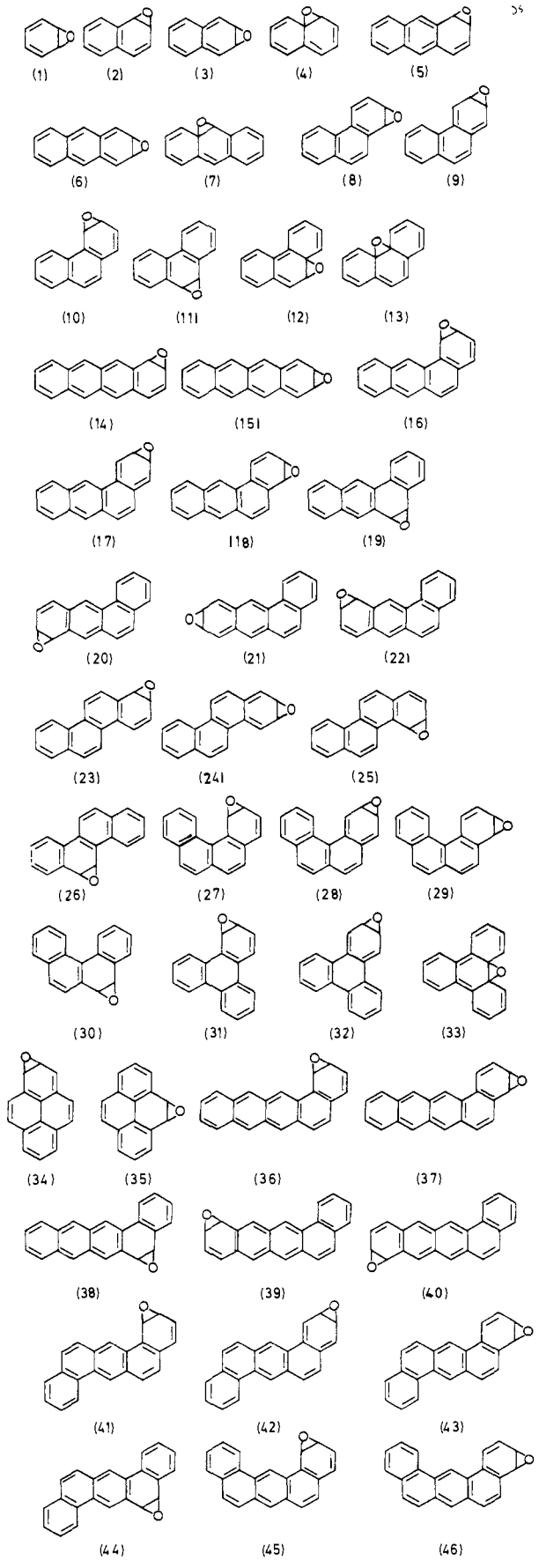


The most plausible mechanism for this racemization involves ring opening to give the corresponding oxepins, which can then reclose to give either enantiomer of the arene oxide (Scheme II). In the first place, this orbital symmetry allowed reaction is well precedented (e.g., in the equilibrium between benzene oxide and the parent oxepin);[15] in the second place, it is difficult to imagine any scheme to achieve the required inversion at both the oxirane carbon atoms that does not involve cleavage of the oxirane C–C bond; finally, in the two cases where $\Delta S^{\ddagger}$ for the racemization has been measured (**23**[10] and **25**[11]), the values (3.6 ± 1.1 and 0.7 ± 0.6 cal/mol·K, respectively) are in the region expected for a unimolecular reaction involving little molecular reorganization and compare well with the value of $\Delta S^{\ddagger}$ (6.6 ± 5.0 cal/mol·K) for the benzene oxide–oxepin isomerization that we have calculated

(1) Present address: Research and Development Division, Gallaher Ltd., Henry Street, Belfast, Northern Ireland.
(2) Boyland, E. *Biochem. Soc. Symp.* **1950**, *5*, 40.
(3) Jerina, D. M.; Daly, J. W.; Witkop, B.; Zaltzman-Nirenberg, P.; Udenfriend, S. *J. Am. Chem. Soc.* **1968**, *90*, 6525.
(4) Boyd, D. R.; Jerina, D. M.; Daly, J. W. *J. Org. Chem.* **1970**, *35*, 3170.
(5) Boyd, D. R.; Gadaginamath, G. S.; Kher, A.; Malone, J. F.; Yagi, H.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2112.
(6) Akhtar, M. N.; Boyd, D. R.; Hamilton, J. G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2437.
(7) Armstrong, R. N.; Kedzierski, B.; Levin, W.; Jerina, D. M. *J. Biol. Chem.* **1981**, *256*, 4726.
(8) Boyd, D. R.; Gadaginamath, G. S.; Sharma, N. D.; Drake, A. F.; Mason, S. F.; Jerina, D. M. *J. Chem. Soc., Perkin Trans 1*, **1981**, 2233.
(9) Boyd, D. R.; Dawson, K. A.; Gadaginamath, G. S.; Hamilton, J. G.; Malone, J. F.; Sharma, N. D. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 94.
(10) Boyd, D. R.; Greene, R. M. E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1535.
(11) Boyd, D. R.; Burnett, M. G.; Greene, R. M. E. *J. Chem. Soc., Chem. Commun.* **1981**, 838; *J. Chem. Soc., Perkin Trans. 1* **1983**, 59.
(12) Boyd, D. R.; Neill, J. D.; Stubbs, M. E. *J. Chem. Soc., Chem. Commun.* **1977**, 873.
(13) Boyd, D. R.; Greene, R. M. E.; Neill, J. D.; Stubbs, M. E.; Yagi, H.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1477.
(14) Boyd, D. R.; Gadaginamath, G. S.; Sharma, N. D.; Yagi, H.; Jerina, D. M., manuscript in preparation.
(15) Vogel, E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385.

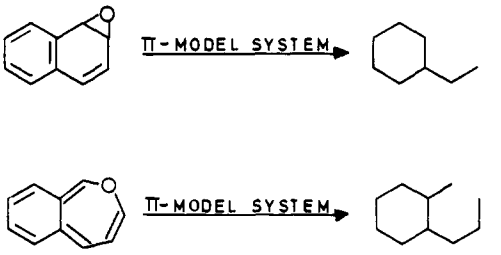
0002-7863/83/1505-2554$01.50/0

Chart I

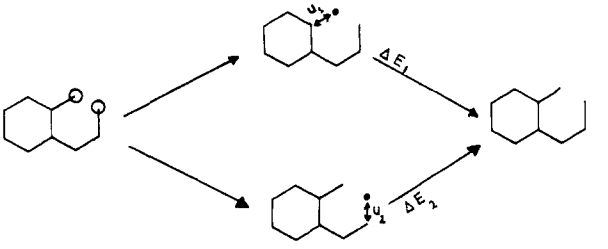


from the data reported by Vogel and Günther.[15] We feel safe in dismissing the theoretical possibility that ring flipping of a nonplanar oxepin constitutes the rate-determining step in this process on the evidence of Hayes et al.[16] that the barrier for this inversion must be extremely low.

Scheme III



Scheme IV



In spite of the plausibility of our postulated mechanism for the observed racemization, it is a fact that high-energy oxepin intermediates (as opposed to stable oxepins) have not so far been detected in the PAH series. We therefore decided to examine the feasibility of such intermediates (Charts I and II) on energetic grounds by means of simple molecular orbital calculations and further to investigate the effect of structural changes on the energetics of isomerization.

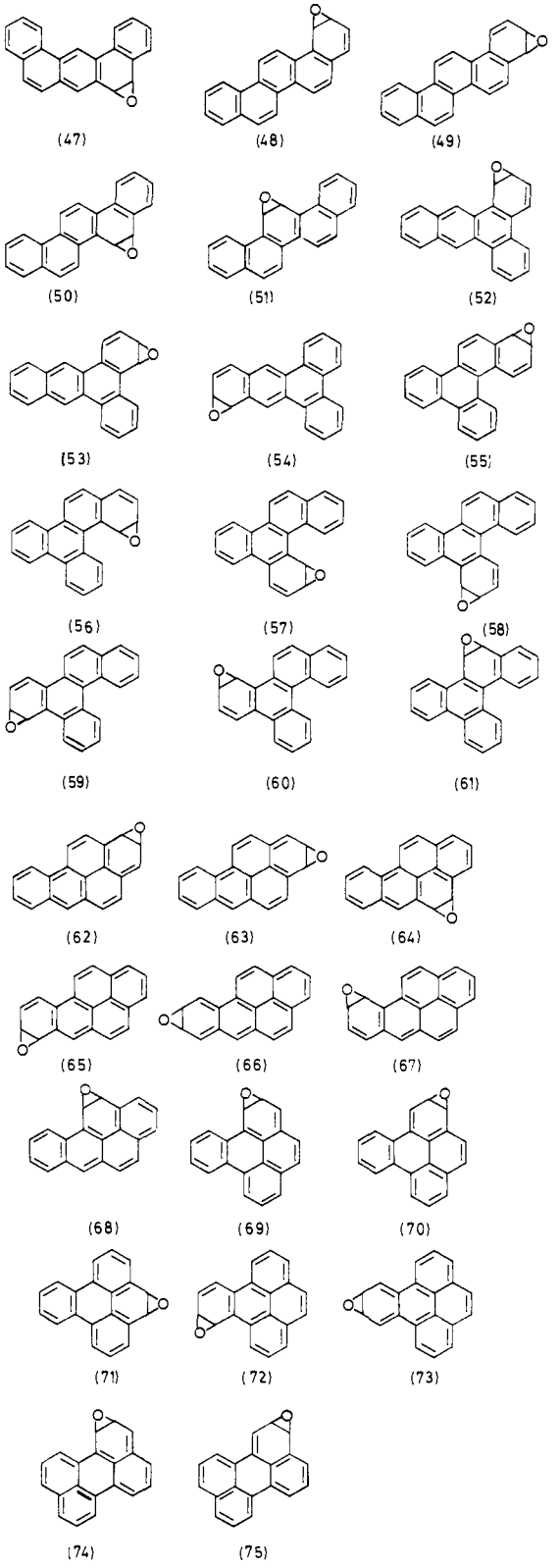
Methods of Calculation

For such orbital symmetry allowed processes, electronic reorganization should be smooth and the influence of the remainder of the molecule on the transition-state energy should be intermediate between its influence on the energies of the oxepin and the arene oxide. Thus, if this is indeed the mechanism, we may expect a close, monotonic correspondence between the activation enthalpy $\Delta H^{\ddagger}$ for the racemization and the electronic energy difference ΔE between the oxepin and the arene oxide. We further expect that since the σ-electron systems change in a similar way for each starting material, for comparative purposes we need consider only the changes in the π-electron systems (with the caveat that in some cases steric effects may be significant). For the arene oxides, the appropriate π-system is clearly that of the corresponding isoelectronic hydrocarbon obtained by deleting the oxygen and two carbon atoms of the oxirane ring. For the oxepins, the potential conjugation of the oxygen atom into the π-system makes it less obvious what we should take as a model; however, semiempirical calculations by Dewar and Trinajstic[17] have shown that the resonance energy of the oxepin is small and (in a series of benzo-condensed oxepins) almost constant. Hess, Schaad, and Holyoke[18] have shown that a very small and nearly constant oxepin resonance energy is consistent with their highly successful Hückel-based approach to aromaticity,[19] which we shall use in our calculations below. We therefore take for the oxepins the π-system obtained by simply deleting the oxygen (Scheme III).

In order to be able to calculate a large number of π-electron energy differences expeditiously, we decided to adopt a perturbational approach. We note that, in each case, the arene oxide model π-system is obtainable by deleting just two orbitals from the oxepin model π-system (Scheme IV). Dewar[20] has presented

(16) Hayes, D. M.; Nelson, S. D.; Garland, W. A.; Kollman, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 1255.
(17) Dewar, M. J. S.; Trinajstic, N. *Tetrahedron* **1970**, *26*, 4269.
(18) Hess, B. A., Jr.; Schaad, L. J.; Holyoke, C. W., Jr. *Tetrahedron* **1972**, *28*, 3657.
(19) Hess, B. A., Jr.; Schaad, L. J. *J. Am. Chem. Soc.* **1971**, *93*, 305.

Chart II

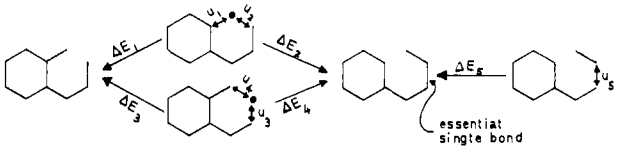


a perturbational method for calculating the energy differences between systems related in this way, which he calls the "paralocalization" method, and which we shall refer to as "method A". This involves calculating the energies of union[21] (ΔE_1 and ΔE_2) of a single orbital with each of the odd alternant π-systems

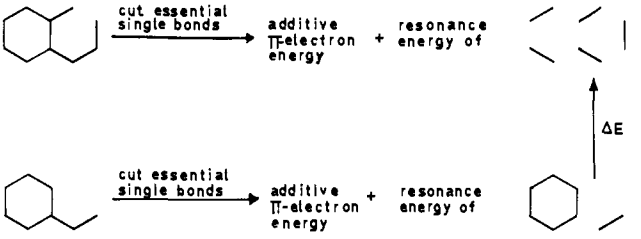
(20) Dewar, M. J. S. "The Molecular Orbital Theory of Organic Chemistry"; McGraw-Hill: New York, 1969; p 323.

(21) For explanations of this and other concepts of PMO theory, see ref 20, Chapter 6, passim.

Scheme V



Scheme VI



obtained by deleting one of the above-mentioned orbitals in the oxepin π-system (Scheme IV); these results are then summed on the assumption that the two first-order perturbations involved are additive, to give a figure that (apart from an additive constant) represents the energy difference between the two π-systems. The additive constant was removed by subtracting the corresponding value calculated for the benzene oxide–oxepin reaction, so directly relating the calculated energy differences to that finely balanced equilibrium[15] for which $\Delta G^\circ \simeq 0$.

We felt, however, that Dewar's justification for this method was not wholly convincing, so we have devised two other methods, equally based on Dewar's perturbational ideas, that seemed more securely based. The first of these (method B) relies on the observation that from each of the above-mentioned odd alternant systems derived by deletion of one orbital from the oxepin model π-systems, we may by alternative unions with one orbital (Scheme V) either (i) regenerate the oxepin model π-system (ΔE_1, ΔE_3) or (ii) generate a vinylogue of the arene oxide π-system (ΔE_2, ΔE_4). We know further, from more sophisticated calculations that have experimental support,[22] that the energy of union of one even alternant system with another (ΔE_5) is small (second order) and very nearly constant, provided the even alternants have no NBMOs and the union generates only essential single bonds (which is always the case for our systems). Therefore, a comparison of the energies for the two processes (i) and (ii) yields the energy difference required ($\Delta E_1 - \Delta E_2$ or $\Delta E_3 - \Delta E_4$); in this case, performing the calculation for the benzene oxide–oxepin reaction shows that the appropriate additive constant is zero. There is one slight complication; unless the system is symmetrical, there will be two different odd alternants that can be used, and these will in general give different results. Reassuringly, these differences were nearly always insignificant, and our practice was simply to average the two values.

The final method used (method C) involves only second-order perturbations, and is more directly related to the well-established localizability of many π-electron systems. The small and nearly constant energies of union of alternant hydrocarbons through essential single bonds can be incorporated into an additive scheme for π-electron energies.[19,22] Therefore, in order to calculate the π-electron energy for an arbitrary system, we need only dissect it at each essential single bond to give a number of irreducible smaller systems that have no essential single bonds (Scheme VI). The total π-energy difference ΔE between any two such systems of the same size is then given by the difference in resonance energy ΔE_R between their respective irreducible components, provided we are careful to use resonance energies consistent with an additive scheme, as discussed by Hess and Schaad.[19] The oxepin and arene oxide π-systems are not of the same size, but they always differ by the same amount (two orbitals), so neglect of this will simply introduce an additive constant. In fact, when we come to relate our results to the benzene oxide–oxepin equilibrium, we find once

(22) Reference 20, pp 208 ff, 173 ff.

Table I. Resonance Energies for Various PAH π-Systems

	exptl, kcal mol^{-1}	SCF, kcal mol^{-1}	HS, β	HS calibrated, kcal mol^{-1}
benzene	20.0	20.0	0.39	20.0
naphthalene	30.5	30.5	0.55	30.5
anthracene	37.8	36.9	0.66	37.7
phenanthrene	44.0	44.6	0.77	44.9
naphthacene			0.75	43.6
benz[*a*]anthracene			0.89	52.8
chrysene	56.3	57.3	0.96	57.4
benzo[*c*]phenanthrene			0.96	57.4
triphenylene	57.0	61.2	1.01	60.7
pyrene	54.2	48.4	0.81	47.6

again that the appropriate additive constant (for the total energy) is zero.

For many of the irreducible systems generated by this method, we have experimental resonance energies or values calculated by SCF methods.[23] However, since we wish to extend our calculations to cases where these figures are not available, we have adopted the following procedure. (i) We have correlated the available experimental and SCF values[23] with the Hess and Schaad (HS) calculations for those compounds, finding an excellent linear relationship (especially with the SCF values) given by $\Delta E_R^{\text{SCF or exptl}} = [\Delta E_R^{\text{HS}}/|\beta| - 0.085] \times 65.6$ kcal/mol where β is the Hückel overlap parameter. The largest deviation seen for the SCF results is 0.8 kcal/mol. Two of the experimental values show larger deviations—triphenylene of 3.7 kcal/mol and pyrene of 6.6 kcal/mol. (ii) All resonance energies were then calculated from the Hess and Schaad values by using this relationship.

Table I compares the various resonance energies and lists the additional ones calculated in this way (where these values are used we refer to our method as C1; the use of the uncalibrated Hess and Schaad values we refer to as method C2).

It might seem at first sight perverse to recalibrate the Hess and Schaad resonance energies, which were, after all, calculated on a supposedly additive model. However, while the Hess and Schaad model is indeed additive for open-chain systems, we see that it is slightly deficient in additivity when we consider essential single-bond unions between cyclic systems. Thus

$$\Delta E_R^{\text{HS}}(\text{biphenyl} \rightarrow 2\text{benzene}) = -0.06\beta \simeq -3 \text{ kcal/mol}$$

$$\Delta E_R^{\text{HS}}(\text{stilbene} \rightarrow 2\text{benzene} + \text{ethylene}) = -0.07\beta \simeq -4 \text{ kcal/mol}$$

$$\Delta E_R^{\text{HS}}(\text{perylene} \rightarrow 2\text{naphthalene}) = -0.13\beta \simeq -7 \text{ kcal/mol}$$

The Dewar additivity model requires these ΔE's to be zero also. If we take the values calibrated as above, we find the ΔE_R values to be respectively +2, +1, and −3 kcal/mol, considerably closer to additivity. We suspect that it would be possible to reparameterize the Hess and Schaad model to improve the additivity for unions between cyclic systems without seriously affecting that for open-chain systems, but for the present we feel that the empirical calibration described above will be satisfactory. We shall see below that there is quite striking evidence from our results that this is so.

Comparison of the Predictions

Table II (supplementary material) lists the predicted resonance energy differences (relative to the benzene oxide system) for a variety of arene oxide–oxepin equilibria according to each of the methods, A, B, C1, and C2. Three of the possible six comparisons between the methods are shown in Figures 1–3, from which the following observations are apparent.

(i) The correlation between methods B and C1, while nonlinear especially at the extremes, is excellent; the deviations from a smooth-fitted curve are rarely in excess of 2 or 3 kcal/mol, and

(23) Reference 20, p 177.

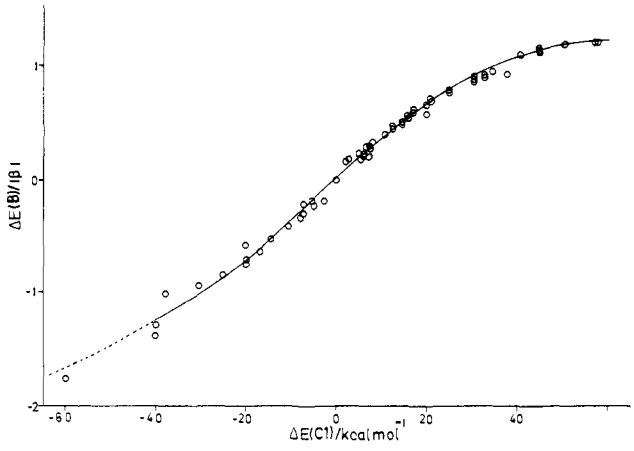


Figure 1.

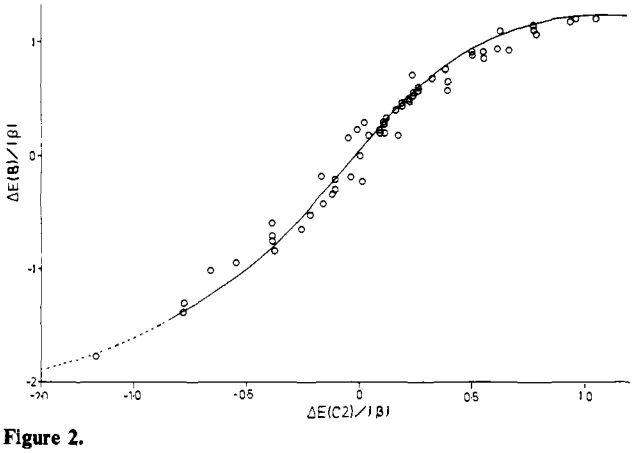


Figure 2.

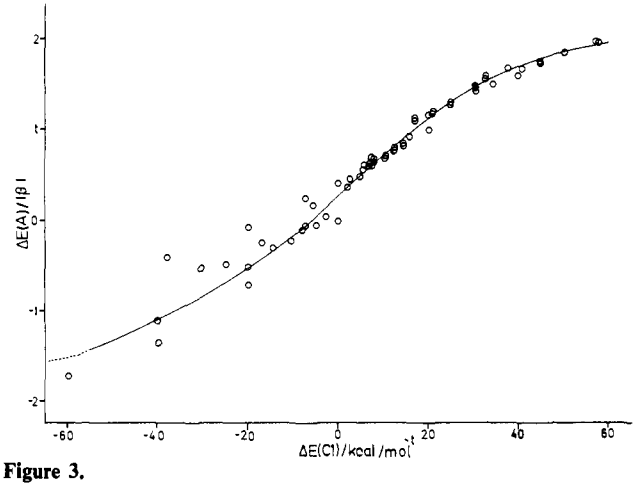


Figure 3.

in the central region less than that. Furthermore the correlation passes through the origin. This result is very encouraging, since the methods are independent of any common assumption apart from the underlying validity of the Hückel model. It seems impossible that such agreement could happen by chance, so we feel confident in the belief that both methods C1 and B give excellent estimates of the resonance energy differences.

(ii) The much poorer correlation between methods B and C2 seems to reflect the nonadditivity problem discussed above for the uncalibrated Hess and Schaad resonance energies and increases our confidence in the calibration procedure described.

(iii) The correlation between methods A and C1 is also poorer than that between methods B and C1, which supports our conjecture that method B should be more reliable than method A. We note in particular that in Figure 3, the best smooth-fitted curve does not pass through the origin.

Table III. Comparison of Experimental and Calculated Results

compd	comments	$[\alpha]_D$, deg	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/mol k	ΔE_R, kcal/mol
33	stable as oxepin[24]				−60.0
12	stable as oxepin[25]				−40.0
13	stable as oxepin[26]				−40.0
3	stable as oxepin[27]				−20.0
4	stable as oxepin[28]				−20.0
1	balanced equilibrium[15]		9.1 ± 0.8	6.6 ± 5.0	0.0
16	no rotation observed[14]				7.2
18	no rotation observed[14]				7.2
10	racemisation observed[12,13]		21.5 (est)[a]		10.5
8	transient rotation[12]				10.5
23	racemisation observed[10]		24.2 ± 0.3	3.6 ± 1.1	14.4
25	racemisation observed[11]		24.6 ± 0.2	0.7 ± 0.6	14.4
65	stable to inversion[5]	+175			17.1
2	stable to inversion[6]	+149			20.0
20	stable to inversion[9]	−115			24.9
22	stable to inversion[8]	+385			24.9
5	stable to inversion[6]	+214			30.5
19	stable to inversion[7,8]	+120			50.5
64	stable to inversion[9]	+123			57.4

[a] Estimated from rate measurements at one temperature, assuming $\Delta S^{\ddagger} = 0$.

Table IV. Predictions for Compounds in Our Data Set

compounds	ΔE_R (C1), kcal/mol	prediction
3, 4, 6, 9, 12, 13, 15, 17, 21, 24, 28, 32, 33, 42, 63, 66, 69, 74		stable as oxepin
	−3	
1, 7, 34, 52, 53, 72, 73		borderline: balanced equilibrium
	3	
16, 18, 31, 36, 37, 41, 43, 45, 46, 57, 58, 59, 60, 62, 70		stable as arene oxide: inversion rapid at ambient temperatures
	8	
none		borderline for observation of inversion at ambient temperatures
	10	
8, 10, 23, 25, 27, 29, 48, 49		inversion measurable at ambient temperatures
	15	
55, 56		borderline for configurational stability at ambient temperatures
	17	
2, 5, 11, 14, 19, 20, 22, 26, 30, 35, 38, 39, 40, 44, 47, 50, 51, 54, 61, 64, 65, 67, 68, 71, 75		configurationally stable at ambient temperatures

The nonlinearity of the plots of method A or B against method C1 is not unexpected; there is no reason why the proportion of the total resonance energy difference represented by the first-order perturbational terms alone should be constant over a wide range of energies. For similar reasons, we are not concerned that the values of β implied for each of the methods A, B, and C2 are different.

Method C1 would seem to be preferable to method B, if only because it gives the energies directly in energy units rather than in units of $|\beta|$. However, where the necessary resonance energies are not readily available, we would be happy to to use method B and calibrate the result by means of Figure 1.

Correspondence between Predictions and Experimental Results

The calculations described above do not by themselves predict rates of racemization or even equilibrium constants: they are useful only for comparative purposes. We have, however, two fixed points, experimentally determinable, against which we can calibrate our predictions. These points are as follows.

(i) The value of ΔE_R corresponding to a finely balanced arene oxide–oxepin equilibrium: This in fact is nearly the case for the parent benzene oxide–oxepin equilibrium where ΔE_R is zero. Thus we can predict that any system for which ΔE_R is substantially less than zero will exist predominantly as the oxepin, and any for which ΔE_R is substantially greater than zero will exist predominantly as the arene oxide. Where ΔE_R is within a few kilocalories per mole of zero, we may expect both isomers to be present in detectable quantity.

(ii) The value of ΔE_R corresponding to a measurably slow inversion of configuration of the arene oxide: From experimental determinations of the racemization rate of chrysene 1,2- and 3,4-epoxides (**23**[10] and **25**)[11] phenanthrene 3,4-epoxide (**10**),[12,13] one can fix this point in the region of $\Delta E_R \simeq 10$ kcal/mol, corresponding to a $\Delta H^{\ddagger}$ of $\simeq 20$ kcal/mol. For any system with ΔE_R substantially less than 10 kcal/mol, racemization should be rapid at ambient temperature (in relation to an experimental time scale of minutes to hours). Where ΔE_R is substantially greater than this, optically active arene oxides should be readily isolable.

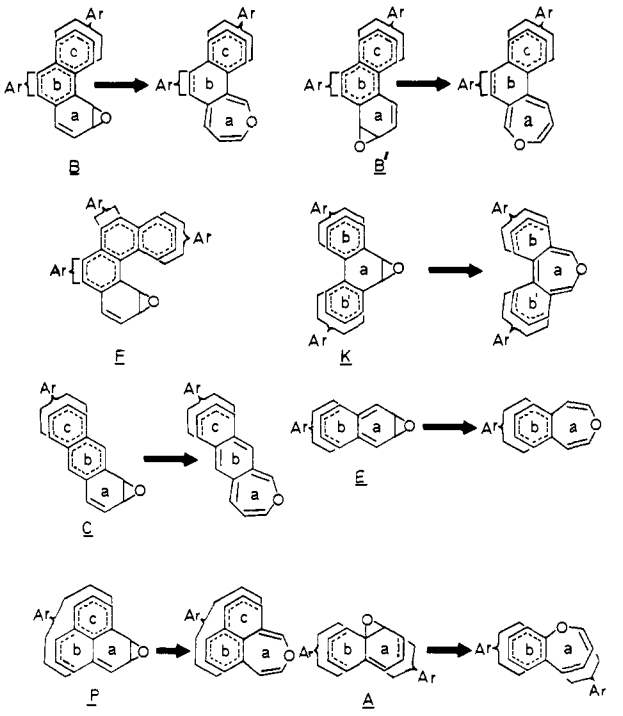
This is well verified by the compounds for which experimental evidence is available (Table III). Thus arene oxides **2**,[6] **5**,[6] **19**,[7,8] **20**,[9] **22**,[8] **64**,[9] and **65**,[5] with $\Delta E_R > 17$ kcal/mol have all been isolated in optically active form (though the last should be racemizable at only slightly elevated temperature provided decomposition reactions do not supervene). On the other hand, arene oxides **16** and **18** with $\Delta E_R \simeq 7$ kcal/mol have defied isolation in optically active form, although they are definitely stable as the arene oxides rather than the valence tautomeric oxepins.[14]

Among the polycyclic oxepins predicted to be stable as such, **33**,[24] **12**,[25] **13**,[26] **3**,[27] and **4**[28] have been synthesized and found to exist as the oxepins.

When we consider the compounds for which racemization takes place at an observable rate (**10**,[12,13] **23**,[10] **25**,[11]), we find a close correspondence between this rate and the predicted ΔE_R. In fact, $\Delta H^{\ddagger}$ (expt) − ΔE_R (calcd) = 10 ± 1 kcal/mol for all compounds where the necessary experiments have been done—including even

(24) Neale, A. J.; Kawlings, T. J.; McCall, E. B. *Tetrahedron* **1965**, *21*, 1299.
(25) Brightwell, N. E.; Griffin, G. W. *J. Chem. Soc., Chem. Commun.* **1973**, 37.
(26) Alam, S. N.; Maclean, D. B. *Can. J. Chem.* **1965**, *43*, 3433.
(27) Dimroth, K.; Pohl, G.; Follmann, H. *Chem. Ber.* **1966**, *99*, 634.
(28) Sondheimer, F.; Shani, A. *J. Am. Chem. Soc.* **1964**, *86*, 3168. Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W. A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 642.

Scheme VII



benzene oxide itself, where $\Delta H^{\ddagger}$ has been determined[15] to be 9.1 kcal/mol in low-temperature experiments.

We note that the entropy of activation plays only a minor role in determining the rate of racemization: where it has been measured, the values are similarly small and positive as we should expect for a reaction of this kind and we see no reason to expect any different behavior in the other cases.

The points of contact established between our predictions of ΔE_R and experimental values of $\Delta H^{\ddagger}$ enable us to set up Table IV; from this and the value of ΔE_R for any arene oxide–oxepin pair we can predict the behavior of that arene oxide with some assurance, granted the absence of unusual steric effects.

Generalizations on the Behavior of Different Structural Types

We may distinguish several types of arene oxides according to whether or not they possess various structural features[29] (Scheme VII): bay region (B), antibay region (B′), fjord region (F), K region (K), C region (C), end region (E), peri region (P), or angular region (A). Clearly, several of these features may be present simultaneously, especially with the larger and more highly condensed skeletons. Benzene and naphthalene 1,2-oxides (**1** and **2**) possess none of these features and should be regarded as special cases.

In bay-region arene oxides (B), provided they do not also contain features K or E, ring opening generally leads to loss of aromaticity in only one ring (b), the rest of the system remaining fully delocalized. The same happens with antibay region oxides (B′), while fjord region compounds (F) are only special cases of B, except for possible steric effects.

The modest loss of aromaticity is reflected in generally low predicted localization energies.

Compounds with feature B (or F) only—**10**, **16**, **25**, **27**, **36**, **41**, **45**, **48**, **56**, **57**: ΔE_R = 5.9–15.8 kcal/mol.

Compounds with feature B′ only—**8**, **18**, **23**, **29**, **37**, **43**, **46**, **49**, **55**: ΔE_R = 5.9–14.4 kcal/mol.

Compounds with both features B and B′—**31**, **52**, **53**, **58**, **59**, **60**, **72**: ΔE_R = 2.3–6.9 kcal/mol.

Note that the presence of both features generally leads to lower localization energies than the presence of either one alone.

(29) Some of these designations are not in established use but have been devised precisely because they have significance in light of the present study. Apart from the bay region/K region distinction, none of the existing commonly made distinctions are important for our purposes.

In K-region arene oxides, at least two aromatic rings (b and b′) must be lost, though the effect of this will be mitigated if B or B′ features are also present. Where a C feature is also present, ΔE_R values tend to be highest of all.

Compound with features K and B (twice)—**51**: ΔE_R = 21.0 kcal/mol.

Compounds with features K and B or K and B′—**26**, **30**, **50**, **61**, **68**: ΔE_R = 24.9–34.4 kcal/mol.

Compounds with feature K only—**11**, **35**, **71**: ΔE_R = 40.0–44.9 kcal/mol.

Compounds with features K and C—**19**, **38**, **44**, **47**, **64**: ΔE_R = 44.9–57.7 kcal/mol.

With C feature alone, again at least two aromatic rings (b and c) must be lost; however, in these systems the two rings are condensed together and their joint loss is less serious than the loss of the two separate rings from K-region arene oxides. Once again, if a B feature is also present, ΔE_R values are reduced.

Compounds with features C and B—**65** and **67**: ΔE_R = 17.1 kcal/mol.

Compounds with feature C alone—**5**, **14**, **20**, **22**, **39**, **40**, **54**: ΔE_R = 20.7–37.7 kcal/mol.

End-region arene oxides (E) generally gain at least one aromatic ring on oxirane ring opening; they therefore show negative ΔE_R values and should be unstable with respect to the corresponding oxepins. Where, however, a peri ring is also present to give features P, a compensation occurs, and small ΔE_R values on either side of zero may be found, leading to the possibility of finely balanced equilibria.

Compounds with feature E—**3**, **6**, **9**, **15**, **17**, **21**, **24**, **28**, **32**, **42**, **66**, **73**: ΔE_R = −37.7 to −2.7 kcal/mol.

Compounds with feature P—**34**, **62**, **63**, **69**, **70**: ΔE_R = −7.2 to +7.2 kcal/mol.

The predictions for **74** and **75** sound a note of warning, however: although they have feature P, they show a ΔE_R of −20.0 and +20.0 kcal/mol, respectively. We can see that this arises from the special circumstance that in perylene the two naphthalene residues are connected by essential single bonds, so that their behavior should be like that of naphthalene 1,2-oxide (**2**) and 2,3-oxide (**3**). Such problems may frequently arise with highly condensed skeletons, so we should be wary of applying these generalizations to them.

Angular-region arene oxides (A) may show any kind of behavior, depending on the other features also present. Because of the lesser importance of these compounds, we shall not attempt a full analysis. Suffice it to say that in the four compounds **4**, **12**, **13**, and **33**, the opening of the oxirane ring generates new aromatic rings and gives ΔE_R = −60.0 to −20.0 kcal/mol, while with **7**, one benzenoid ring is simply exchanged for another, so that ΔE_R = 0. Because in these compounds the oxirane ring forms a spiro junction with the rest of the carbon skeleton, we may also expect quite different steric effects with angular-region arene oxides, reducing our confidence in these predictions.

Registry No. **1**, 1488-25-1; **2**, 17180-88-0; **3**, 84849-76-3; **4**, 175-49-5; **5**, 84849-77-4; **6**, 84849-78-5; **8**, 39834-44-1; **9**, 84849-79-6; **10**, 39834-45-2; **11**, 585-08-0; **12**, 84849-80-9; **13**, 41163-08-0; **14**, 84849-81-0; **15**, 84849-82-1; **16**, 84849-83-2; **17**, 84849-84-3; **18**, 84849-85-4; **19**, 962-32-3; **20**, 34501-55-8; **21**, 36777-53-4; **22**, 84894-01-9; **23**, 84894-02-0; **24**, 84849-86-5; **25**, 84894-03-1; **26**, 15131-84-7; **27**, 84849-87-6; **28**, 84849-88-7; **29**, 62987-63-7; **30**, 60692-90-2; **31**, 84849-89-8; **32**, 84849-90-1; **33**, 84849-91-2; **34**, 84849-92-3; **35**, 37496-00-7; **36**, 84849-93-4; **37**, 84849-94-5; **38**, 84849-95-6; **39**, 84849-96-7; **40**, 84849-97-8; **41**, 84849-98-9; **42**, 84849-99-0; **43**, 84850-00-0; **44**, 1421-85-8; **45**, 84850-01-1; **46**, 84850-02-2; **47**, 84850-03-3; **48**, 84850-04-4; **49**, 84850-05-5; **50**, 84850-06-6; **51**, 84850-07-7; **52**, 84850-08-8; **53**, 84850-09-9; **54**, 39081-12-4; **55**, 84850-10-2; **56**, 84850-11-3; **57**, 84850-12-4; **58**, 84850-13-5; **59**, 84850-14-6; **60**, 84850-15-7; **61**, 84850-16-8; **62**, 72955-61-4; **63**, 72955-62-5; **64**, 37574-47-3; **65**, 36504-65-1; **66**, 84850-17-9; **67**, 36504-66-2; **68**, 60448-19-3; **69**, 84850-18-0; **70**, 84850-19-1; **71**, 71207-06-2; **72**, 84850-20-4; **73**, 84850-21-5; **74**, 84850-22-6; **75**, 84850-23-7.

Supplementary Material Available: Calculated energy differences for the arene oxide–oxepin equilibria (3 pages). Ordering information may be found on any current masthead page.