

Similarity Approach to Chemical Reactivity. Regioselectivity in Pericyclic Reactions

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Received January 31, 1997[®]

The similarity approach recently proposed as a new universal means of the study of pericyclic reactivity was applied to the study of the phenomenon of regioselectivity. It has been shown that even within a simple HMO model the approach is able to predict the preferred regiochemistry of various types of pericyclic reactions like polar and semipolar Diels–Alder reactions, 2 + 2 additions, etc. In contrast to alternative perturbational theories of regioselectivity this approach is in most cases able to predict also whether the reaction proceeds as a concerted one-step process or whether some biradical or zwitterionic intermediates are involved.

INTRODUCTION

One of the most important questions connected with the problem of substituent effect in pericyclic reactions is the question of prediction and interpretation of the preferred direction of reaction in the case of several reaction products differing by the position of the substituents. This problem of the so-called regioselectivity was theoretically discussed in several studies,^{1–10} which resulted in several techniques allowing the problem to be systematically solved. The majority of these studies is based on the perturbation or FMO theory where the preferred direction of reaction is deduced from the expressions characterizing the interactions between selected, usually frontier molecular orbitals. As a typical example may serve, e.g., the pioneering studies by Houk, Herndon, and Epitotis.^{1,5–7} All these studies are, however, based on the assumption of a concerted mechanism where the newly formed bonds are created more or less synchronously. Such an assumption need not, however, be entirely justified since a number of cases were also reported whose explanation can be more consistently given in terms of a nonconcerted reaction mechanism involving various biradical or zwitterionic intermediates.^{11–13} Although the perturbational approaches can in principle be modified to cases of such nonconcerted reaction paths, the need for the a priori knowledge of the reaction mechanism necessary for the decision as to which of the corresponding perturbational expressions is to be applied in a given particular case makes the practical use of the above approach a bit complicated.

In this connection it is therefore interesting that just the question of the preferred reaction mechanism of pericyclic reactions (one-step concerted vs nonconcerted stepwise) can successfully be solved within the framework of the recently proposed topological theory of chemical reactivity based on the so-called similarity indices.^{14–16}

Our aim in this study is to follow up with the results of our previous studies in this field and to demonstrate that the similarity approach recently applied to the rationalization of various aspects of pericyclic reactivity^{17,18} can be used for the prediction of regioselectivity as well. Although the predicting power of the proposed approach is comparable to that of usual FMO techniques, its greatest advantage in comparison with other alternative approaches consists in that

the preliminary knowledge of the reaction mechanism required by other models is not necessary here since the determination of the preferred reaction mechanism is a natural byproduct of the determination of the preferred regiochemical course of the reaction.

THEORETICAL

The proposed criterion is based on the recently introduced topological approach arising from the exploitation of the so-called similarity index.¹⁴ This index, originally introduced into the chemical theory by Polansky and Carbo,^{19,20} was recently generalized by us for the application to chemical reactivity theory.^{15–18} Within the framework of this generalization, the original definition expressing the similarity of two isoelectronic molecules A and B in terms of corresponding density matrices $\rho_A(1), \rho_B(1)$

$$r_{AB} = \frac{\int \rho_A(1) \rho_B(1) d\tau}{(\int \rho_A^2(1) d\tau)^{1/2} (\int \rho_B^2(1) d\tau)^{1/2}} \quad (1)$$

was rewritten in the form 2, where the molecules A and B, the similarity of which we are interested in, are naturally identified with the reactant R and the product P of a given reaction and where the prime over the matrix

$$r_{RP} = \frac{\text{Tr} \mathbf{P}_R' \overline{\mathbf{P}}_P}{N_{RP}} \quad (2)$$

denotes the similarity transformation³

$$\overline{\mathbf{P}}_P = \mathbf{T}^{-1} \mathbf{P}_P \mathbf{T} \quad (3)$$

This transformation enters into the formalism from the closely related overlap determinant method²¹ and its aim, the conversion of density matrix \mathbf{P}_P into the same AO basis as describing the matrix \mathbf{P}_R , is analogous to what is played in the overlap determinant method by the so-called assigning tables. The most important feature of the transformation matrix \mathbf{T} is that its form depends on the actual reaction mechanism of the transformation $R \rightarrow P$. Via this matrix the possibility to discriminate between allowed and forbidden reactions can thus be introduced.

[®] Abstract published in *Advance ACS Abstracts*, June 15, 1997.

The physical meaning of similarity index was analyzed in our study²² where we demonstrated that the values of r_{RP} are directly related to the extent of electron reorganization accompanying the transformation of the reactant into the product. Generally it holds that higher values of r_{RP} are connected with smaller reorganization and vice versa. On the basis of this interpretation, the practical use of the above index arises from the simple intuitive analogy between the extent of electron reorganization and the ease of the reaction. This analogy, expressing the physical meaning of the so-called least-motion principle,²³ finds its natural reflection in that the extent of electron reorganization is generally lower in allowed reactions than in the forbidden ones.

The above relation between the magnitude of r_{RP} and the ease of the reaction is then also a general methodological basis for the proposed extension of the similarity approach to the study of regioselectivity. The philosophy of this extension is very simple and consists in the determination of the values of similarity indices for a series of reactions on various substituted skeletons and in the comparison of corresponding values for several regiochemically different reaction paths. The preferred direction of the reaction is then the one for which the extent of electron reorganization is the least.

In connection with the practical use of the proposed approach it is, however, necessary to mention yet another important aspect. This aspect is that the model based on the similarity index r_{RP} is inherently predestined for the study of processes, where the transformation $R \rightarrow P$ proceeds concertedly in one elementary step. Although the majority of existing regioselectivity models is formulated just for this class of reactions,^{1-7,10} the existence of certain exceptions which can more easily be explained by the participation of intermediates suggests that without explicit inclusion of nonconcerted reaction paths the theories of regioselectivity are necessarily only one-sided. In this connection it is therefore important that the similarity approach, originally formulated for concerted processes, can simply be generalized to nonconcerted reactions as well. In the case of pericyclic reactions these nonconcerted paths are represented by the following two-step reaction scheme 4 in which, depending on the polarity of the system, the intermediate has a character of biradical or zwitterionic species.



The philosophy of generalization of similarity approach to this scheme is very simple and consists in the characterization of the total extent of electron reorganization in the process 4 in terms of particular similarity indices r_{RI} and r_{IP} for each individual reaction step. In a previous study¹⁶ we demonstrated that the total extent of reorganization in process 4 can be given approximately by the quantity $\xi = r_{RI} \cdot r_{IP}$. On the basis of this value and of its comparison with the value of r_{RP} for the direct concerted process, the relative ease of concerted and nonconcerted reaction paths can be estimated. Generally it holds that where the value of r_{RP} is greater than the value of the product $r_{RI} \cdot r_{IP}$, the preference of the concerted mechanism can be expected. On the other hand, the reversal of the above inequality suggests the preference of the stepwise reaction path. On the basis of this simple criterion the prediction of regioselectivity in concerted and stepwise mechanisms is straightforward and consists in the comparison of similarity indices r_{RP} and ξ

Table 1. Calculated Values of Similarity Indices for Polar Diels–Alder Addition of Donor 2-Substituted Butadienes with Acceptor Substituted Ethenes in Dependence on the Value of Coulombic Integral α (in β Units) Modeling the Substitution^a

product	α_D	α_A	r_{RP}	r_{RB1}	r_{B1P}	ξ^{B1}	r_{RB2}	r_{B2P}	ξ^{B2}
para	-2	2	0.621	0.767	0.860	0.659	0.797	0.824	0.657
	-1	1	0.595	0.739	0.860	0.635	0.761	0.806	0.613
meta	-2	2	0.597	0.702	0.880	0.622	0.822	0.754	0.619
	-1	1	0.580	0.678	0.853	0.578	0.720	0.867	0.624
nonsubst	0	0	0.575	0.721	0.859	0.619	0.721	0.859	0.619

^a Comparison of concerted and stepwise biradical mechanism.

Table 2. Calculated Values of Similarity Indices for Polar Diels–Alder Addition of Donor 2-Substituted Butadienes with Acceptor Substituted Ethenes in Dependence on the Value of Coulombic Integral α (in β Units) Modeling the Substitution^a

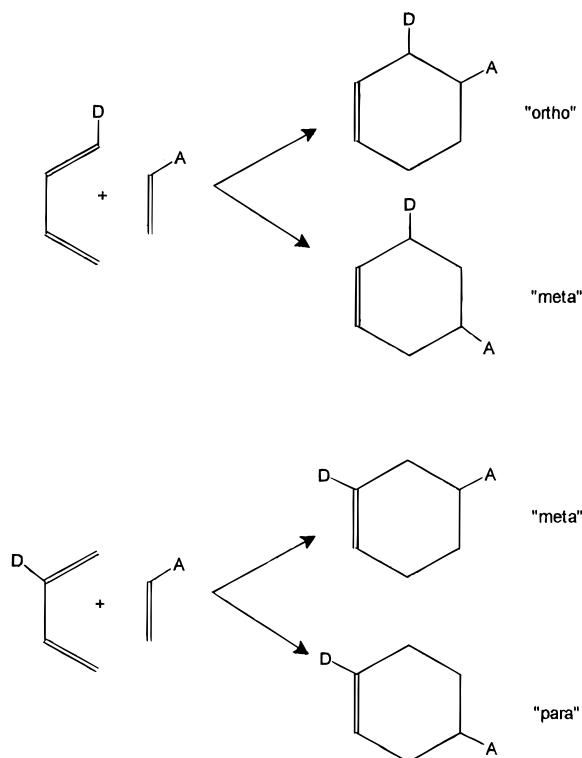
product	α_D	α_A	r_{RP}	r_{RZ1}	r_{Z1P}	ξ^{Z1}	r_{RZ2}	r_{Z2P}	ξ^{Z2}
para	-2	2	0.621	0.631	0.766	0.491	0.755	0.848	0.640
	-1	1	0.595	0.626	0.766	0.489	0.733	0.820	0.601
meta	-2	2	0.597	0.704	0.845	0.595	0.656	0.771	0.505
	-1	1	0.580	0.683	0.816	0.557	0.661	0.771	0.509
nonsubst	0	0	0.575	0.658	0.785	0.516	0.658	0.785	0.516

^a Comparison of concerted and stepwise zwitterionic mechanism.

for various regiochemically different reaction paths and in the subsequent selection of that one for which the extent of electron reorganization is the least.

Before demonstrating the practical application of this approach it is necessary to say here a few words about the problem of modeling the substituent effect. Because of the topological nature of the overlap determinant method on which our similarity approach is based, the above formalism is formulated for similarity indices derived from the simple HMO density matrices so that the substituent effect has also to be modeled consistently. One possibility is to use recommended HMO parameters for a given substituent. In this way it would be, in principle, possible to perform the analysis for any particular system. It is true, however, that such a straightforward approach clearly relies on the reliability of the parameter set used. For that reason we prefer to use an alternative approach in which the substitution is modeled not by a particular value of coulombic (and resonance) integrals but by systematically varying these integrals over a certain region. In this way we lose, of course, a straightforward assignment between a particular value of parameter and a certain specific substituent, but, on the other hand, we gain the possibility of analyzing and predicting general trends which for chemistry are frequently more valuable than the isolated knowledge on a isolated particular system. This aspect is especially important if we realize that the present state of computational quantum chemistry allows one to apply its methods just to such particular systems so that the possibility of investigating these systems becomes reality. Despite the fact that this is true in principle, the real situation is frequently much more complicated since there are still some systems where even the best contemporary methods are not reliable enough. The typical example of such a system is, e.g., the Diels–Alder reaction whose mechanism is still the subject of discussions²⁴⁻³¹ and especially recent experimental findings of predominance of nonconcerted mechanisms represent a serious challenge to existing quantum chemical predictions.³² This implies that even the best direct methods, if applied to isolated particular systems, still do not provide a sufficient

Scheme 1



guarantee of the absolute reliability so that the predictions of general qualitative trends, which fortunately is much less demanding on the quality of the methods used, may still be desirable and useful. The presented similarity model is just a representative of such a simple qualitative approach.

In the following part the practical use of the proposed approach will be demonstrated on the analysis of several selected pericyclic reactions in which the substitution was modeled by the systematic variation of the integrals. The calculated values of similarity indices r_{RP} (α) and $\xi(\alpha)$ for polar and semipolar Diels–Alder reactions, 2 + 2 additions, etc. are collected in Tables 1 and 2 and in Schemes 3, 5, 7, 8, 10, and 12.

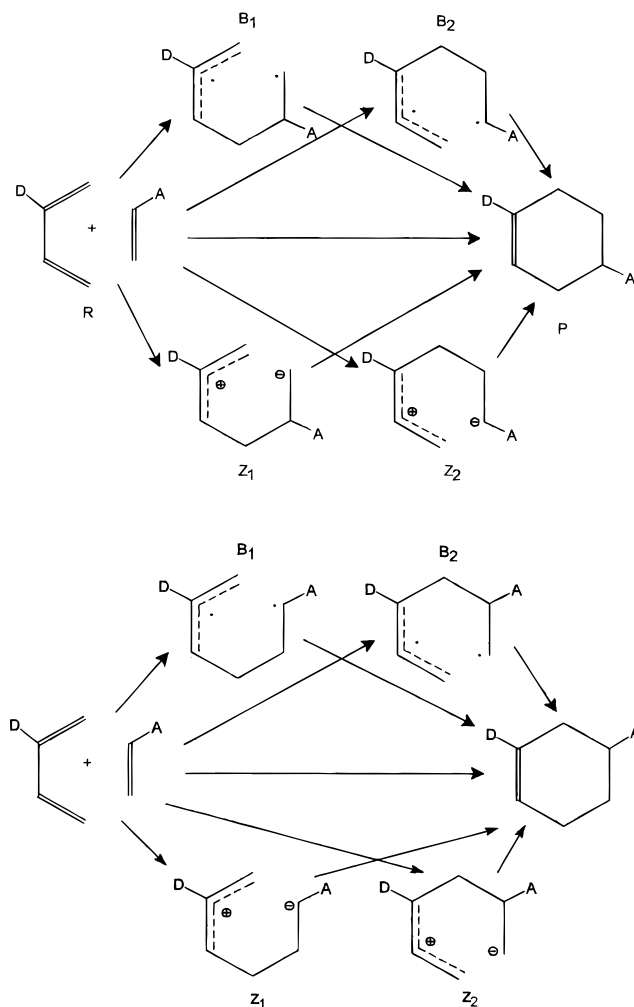
RESULTS AND DISCUSSION

As an example demonstrating the possibilities of the above approach let us discuss first the case of the so-called polar Diels–Alder reaction which is characteristic of the presence of donor substitution on diene and acceptor substitution on the dienophile component of the reaction. Depending on the actual position of substitution two alternative reactions exist (Scheme 1). Each of these reactions can in principle lead to two different regioisomers but usually one of them prevails. In our case the preferred reaction products correspond to “ortho” and “para” isomers.^{1,5–7,32} The prediction of the preferred reaction product says, however, nothing about the actual mechanism of its formation. Generally two alternative mechanisms can be proposed which proceed either as a concerted one-step or a nonconcerted two-step process involving biradical or zwitterionic intermediates.

These alternative mechanisms are summarized in Scheme 2, and the main goal of the presented model is to evaluate the ease of each of the possible reaction paths with their regiochemical consequences by comparing the corresponding similarity indices.

In this way it is possible to predict both the preferred regiochemical product and, also, the preferred mechanism

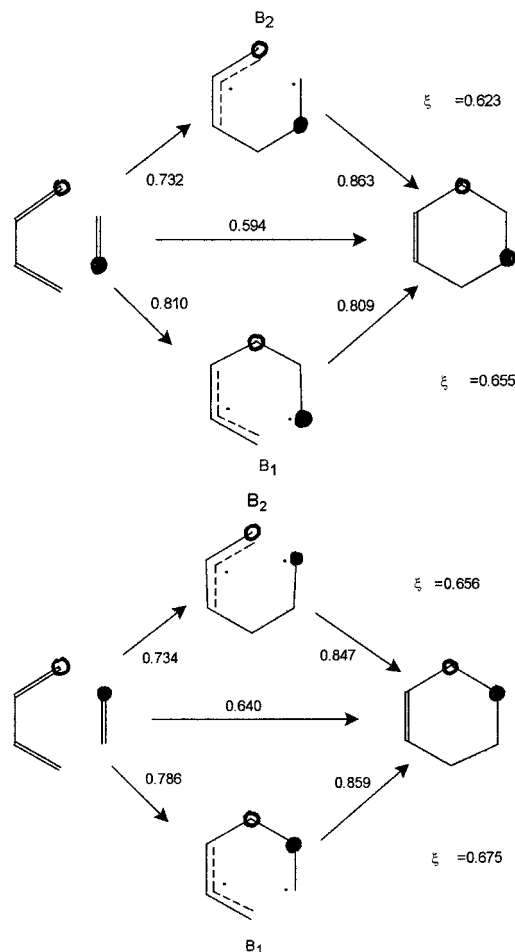
Scheme 2



of its formation. Moreover, since as it is stated above the introduction of the substitution can be modeled by the change of the corresponding Coulombic integral α , the calculation of similarity indices for the systematically varied values of α can give us an idea of how the regiochemistry and the mechanism of the process can be influenced by the polarity of the system. In our case we have performed such a systematic analysis of the reaction Scheme 2 for α ranging from 0β to 2β (for acceptor substitution) and from 0β to -2β (for donor substitution). The resulting similarity indices are summarized in Tables 1 and 2.

Let us now discuss some general conclusion which can be deduced from the tables. First of all it is possible to see that irrespective of the reaction mechanism the values of the similarity indices r_{RP} and ξ are generally higher for substituted systems than for the parent one. This implies that the polar Diels–Alder reactions should generally be easier than the parent one, and this conclusion is in complete agreement both with the experimental observations^{32,33} and with the theoretical predictions.^{24,34} After this basic qualitative test let us look now at what the approach predicts for the regiochemistry of the process. Here it is possible to see that in keeping with the experimental observations, the formation of para regioisomer is indeed preferred over the “meta” one, and this preference can be expected for both the concerted and the stepwise mechanism. This result is very important since it demonstrates that the philosophy frequently used with perturbational approaches according to which the agreement between the experimental and theoretical regiochemistry

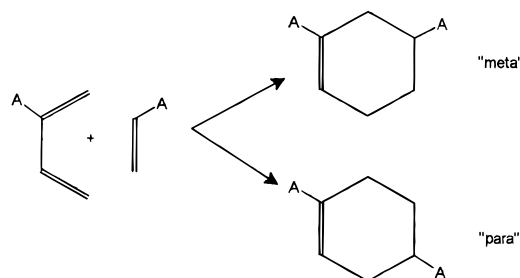
Scheme 3



derived for one specific reaction mechanism (concerted or stepwise) ensures that the reaction proceeds by that mechanism can be misleading. In fact, the observed regiochemistry may be compatible with both of them, and perturbational theory gives us no recipe as to how to decide between them. On the other hand, the proposed similarity model naturally also solves this important mechanistic question. Let us look from this point of view at the values in Tables 1 and 2. As it is possible to see the reaction leading to the preferred para isomer can be expected to proceed by a nonconcerted mechanism ($\xi > r_{RP}$), and the biradical pathway seems to be slightly more favorable than the zwitterionic one ($\xi^B > \xi^Z$). The difference between ξ^B and ξ^Z decreases, however, with increasing $|\alpha|$ which suggests that in very polar systems the zwitterionic mechanism may become preferred. In this connection it is also worth remembering that zwitterionic reaction paths can generally be expected to be sensitive to solvent effect so that the additional stabilization of zwitterionic reaction paths can be expected in polar solvents. Although the study of the solvent effect is not reported here, the methodology of the similarity approach can quite straightforwardly be applied in this case as well. Only what is necessary is the knowledge of the density matrices generated by appropriate quantum chemical method with an explicitly included solvent effect. This, of course, is not possible within a simple HMO method, but the simplest form of the PPP approach with solvent effect described, e.g., via the solvation model by Miertus and Klopman,^{35,36} could be a reasonable alternative.

The dominance of the two-step mechanism is very interesting since the experimental data on substituted systems

Scheme 4



are usually interpreted in terms of a nonconcerted two-step mechanism.^{8,11,13,25-27} The nonconcerted reaction mechanism is also predicted to be more favorable for other polar Diels-Alder systems, and it is possible to see from the Scheme 3 that the similarity approach agrees with the observations in correctly predicting the regiochemistry of the process (prevalance of ortho regioisomer).

Having demonstrated the applicability of the approach to polar Diels-Alder reactions let us analyze, in a similar way, also the so-called semipolar Diels-Alder reactions,⁷ which are the systems in which the substitution on both diene and dienophilic components is of the same nature (both either donors or acceptors). This type of reaction was analyzed by in the study,⁷ and it was predicted that if the reaction proceeds by a concerted mechanism, then the formation of the meta regioisomer should be preferred. This theoretical prediction is not, however, compatible with experimental observations since the ortho and para regioisomers prevail. It was thus proposed that the discrepancy could come from the fact that the mechanism of the reaction is not concerted but stepwise.

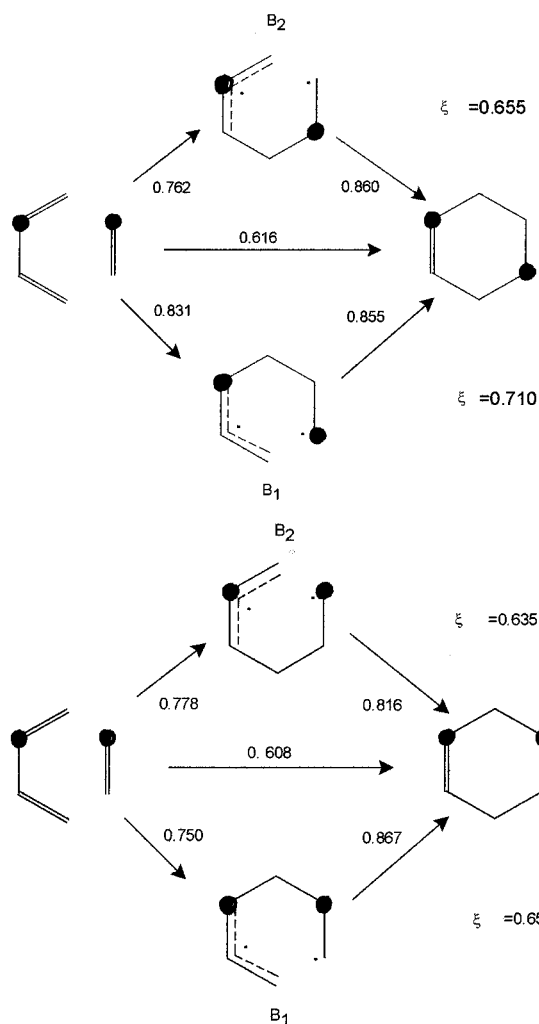
Such an "explanation" is not, however, very convincing since, as it was shown above, the regiochemical outcome of both concerted and nonconcerted mechanisms need not necessarily be opposite. This implies, however, that without explicit evaluation of regiochemical consequences of nonconcerted reaction mechanisms the above explanation is not quite satisfactory. In the following part we are going to demonstrate that the proposed similarity approach is able to remedy the disadvantage of the above mentioned perturbational model and to predict both the reaction mechanism and the preferred regiochemistry. As an example let us report the results of the analysis for the system (Scheme 4).

The substitution was again modeled by the change of Coulombic integral α on the appropriate centers. The results of this analysis are summarized in Scheme 5 in which the values correspond to a particular choice of acceptor substituent with $\alpha = 1/\beta$. As it is possible to see, the most easy of all possible reaction paths corresponds to a nonconcerted biradical pathway (via intermediate B_1) which leads to a para regioisomeric product. We can thus see that contrary to alternative perturbational approaches the similarity model predicts the regiochemistry of the process consistently with the reaction mechanism.

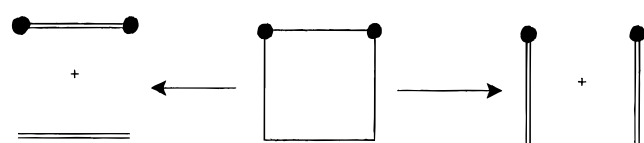
In a similar way it would be possible to analyze also other pericyclic reactions. As an example of such a use let us analyze, in the following part, the thermal fragmentation of 1,2-substituted cyclobutanes. This reaction can in principle yield two regiochemically different products (Scheme 6) but experimentally observed is only the symmetrical fragmentation leading to two molecules of monosubstituted ethenes.

In order to determine the theoretical prediction of regioselectivity, all possible concerted and nonconcerted reaction

Scheme 5



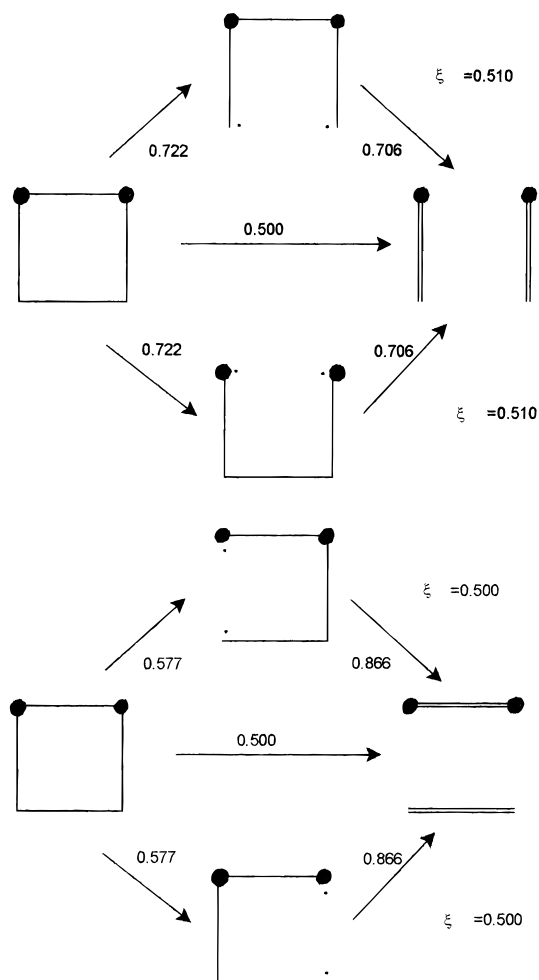
Scheme 6



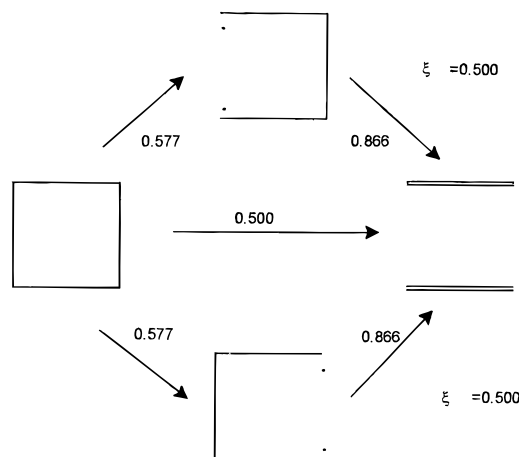
mechanisms have to be taken again into account. The results of such analysis are summarized in Scheme 7. The substitution was again modeled by the change of Coulombic integral α on appropriate centers, and the values in the scheme correspond to a particular choice of donor substitution with $\alpha = -1\beta$. This could correspond, e.g., to the fragmentation of 1,2-dialkylcyclobutanes.

Let us discuss now the main conclusions resulting from this scheme. First what can be seen is that the values of similarity indices for the concerted process are not influenced by the substitution and remain the same as for the parent unsubstituted system (Scheme 8). This suggests that the concerted reaction should not be practically influenced by the substitution. This theoretical prediction is, however, in contradiction to what is observed since the experimental activation barriers for the symmetrical fragmentation of alkylcyclobutanes are considerably lower compared to parent cyclobutane.³⁷ The natural explanation of this discrepancy comes from the values of the indices ξ which demonstrate that the only alternative supporting the experimental observations is the nonconcerted reaction mechanism leading, moreover, just to the symmetrical fragmentation.

Scheme 7



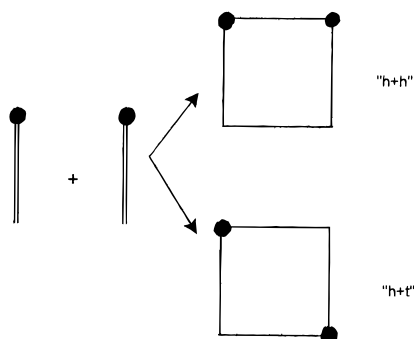
Scheme 8



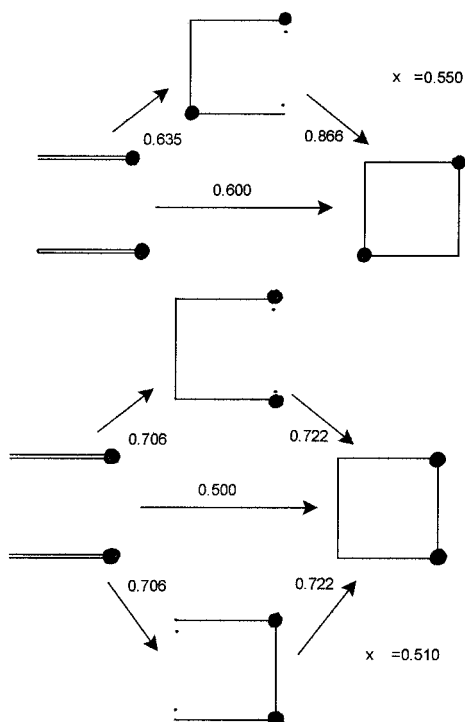
The problem of the fragmentation of bisubstituted cyclobutanes is also closely related to the question of regioselectivity of the reversed reaction, the so-called nonpolar 2 + 2 addition. This reaction can in principle proceed by two regiochemically different paths leading to the products of "h + h" and "h + t" type (Scheme 9).

Regioselectivity of these reactions was analyzed by Epiotis⁷ who found that the formation of h + h products is to be expected if the reaction is nonconcerted, while for the concerted reaction the formation of the h + t product is to be preferred. The fact that a majority of such reactions yield h + h regioisomeric products was then regarded as an indication of the nonconcerted nature of the process. Let

Scheme 9

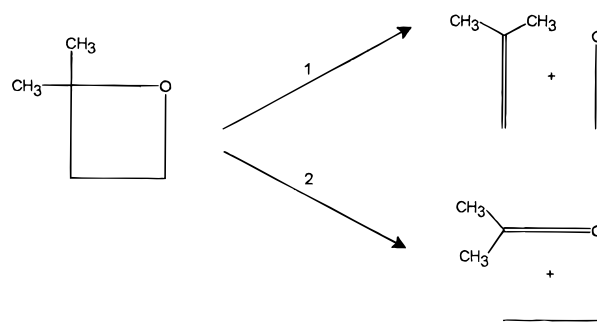


Scheme 10

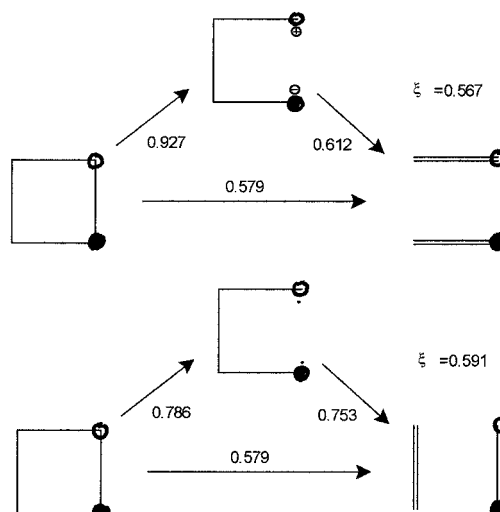


us discuss now these predictions in the light of our approach. As it is possible to see from Scheme 10 (calculated again for the particular value of $\alpha = 1\beta$ which could correspond, e.g., to the dimerization of acrylonitrile), the original prediction of the preferred formation of $h + t$ products by a concerted reaction as well as the nonconcerted nature of the process leading to $h + h$ products is completely reproduced by our model. In spite of this correspondence, the situation is, however, a bit more complex and deserves a special comment. The problem is that from the point of view of the least motion principle the formation of $h + t$ products is more favorable than the formation of $h + h$ ones not only by concerted mechanism but also by stepwise reaction paths so that the question naturally arises as to why the formation of $h + h$ products is ever observed. For this discrepancy neither the Epiotis theory nor our approach offers an explanation. Some doubts remain, however, also for $h + t$ additions since the original arguments rationalizing the occurrence of this reaction in the dimerization of ketenes by more favorable steric conditions facilitating the allowed $s + a$ concerted mechanism are not entirely convincing. Thus, e.g., it was observed that the cyclobutadienones, predicted to be the preferred products of $h + t$ addition, are formed as the main products only in the dimerizations of ketoketenes,³⁸ while in mixed dimerizations with aldoketenes the reaction usually yields the isomeric oxetanones.³⁹

Scheme 11



Scheme 12



Moreover, the additions are reported in which the reactions are completely nonregiospecific and result in the formation of 1:1 mixture of cyclobutandiones and oxetanones.⁴⁰ An uncertainty exists also in the question of the reaction mechanism since both nonconcerted and concerted reaction paths were observed.^{38,39,41} The existence of the allowed $s + a$ reaction mechanism usually regarded as a reasonable model of a concerted reaction path in the ketene dimerization was also questioned by Seidl and Schaefer.⁴² This suggests that the attempts to support the theoretical predictions of regioselectivity in $2 + 2$ cycloadditions by examples from the ketene dimerizations⁷ are not apparently quite justified and may be misleading. Further tests on regioselectivity of "normal" $2 + 2$ reactions are thus still necessary to evaluate the applicability of existing theories.

An example of such a test may concern, e.g., the mechanism of thermal (laser induced) fragmentation of 2,2-dimethyloxetane.⁴³ The reaction proceeds by two unimolecular paths (Scheme 11) which were found to involve different reaction mechanisms.

Thus while reaction 1 is concerted, the fragmentation path 2 is more likely to be stepwise process involving biradical intermediate. Moreover, the activation barrier for the process 1 was found to be lower than for the fragmentation 2. Let us confront now these experimental observations with the theoretical predictions of our model. The mechanistic scheme involving the values of similarity indices for both alternative reaction paths are summarized in Scheme 12. The values were again generated by a simple HMO model, the donor methyl-substitution and electron accepting oxetane oxygen were modeled by $\alpha = -1\beta$ and $\alpha = 1\beta$, respectively. As it is possible to see the concerted fragmentation 1 seems

indeed to be preferred by the model ($r_{RP} > \xi$) as well as the stepwise mechanism of process 2.

Although the mechanism and the regiochemistry of both reaction paths is correctly reproduced by the approach, there are, however, still some other questions which remain unsolved. Thus, e.g., the comparison of similarity indices for the preferred reaction mechanism of both reaction paths seems to suggest that fragmentation 2 should be easier than fragmentation 1 but this expectation is not consistent with the experimental activation barriers. The situation is thus similar to what was reported above for the comparison of $h + h$ and $h + t$ dimerizations, and, like there, no explanation can be offered within both Epiotis theory and our model.

Despite these limitations it is perhaps possible to conclude that the presented examples of successful rationalization of regioselectivity, together with previously reported applications, allow us to conclude that the similarity approach represents a new surprisingly universal means of analysis of pericyclic reactivity, and we believe that it is just this universality which makes the similarity model an efficient new approach to the study of chemical reactivity.

In this connection it is, however, important to emphasize that the aim of this simple approach is not to substitute sophisticated MO calculations but rather to give a synthetic organic chemist a simple and quick enough means of the analysis and rationalization of various aspects of pericyclic reactivity and thus to help him in the design of optimal strategy for the synthesis of the desired products. In this respect we believe that the simplicity and easy algorithmization makes the similarity approach a potential candidate for inclusion into the programs for the computer designed synthesis.

ACKNOWLEDGMENT

This study was supported by the grant of the Grant Agency of the Czech Republic No: 203/95/0650. This support is gratefully acknowledged by the author.

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