SIMILARITY APPROACH TO CHEMICAL REACTIVITY. SUBSTITUENT EFFECT IN PERICYCLIC REACTIONS

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Dedicated to Professor Václav Horák on the occasion of his 70th birthday.

The recently introduced similarity approach to chemical reactivity was applied to the systematic investigation of the substituent effect on pericyclic reactivity. The agreement of the resulting predictions with available experimental or theoretical data confirms that the basic features of the substituent effect are correctly reproduced by the model.

Although the basic features of pericyclic reactivity such as e.g. the remarkable difference in the steric course of the allowed and forbidden reactions are generally well reproduced by the Woodward–Hoffmann rules[1] and the closely related correlation diagrams[2], a number of other more subtle effects, the description of which exceeds the scope of these original techniques also exists. An example in this respect would be the problems connected with the effect of substituents on the rate, mechanism, and regioselectivity of pericyclic reactions. Because of importance of these questions, the problem of substituent effect has been the subject of numerous investigations. Most of these studies are based on the application of perturbation or FMO theory[3 – 13], the philosophy of which, however, is completely different from the philosophy of the original Woodward–Hoffmann rules. We are thus in a position that one approach, the Woodward–Hoffmann rules and correlation diagrams, deals with one aspect of pericyclic reactivity, whereas the other aspects are solved by an approach that is conceptually rather different. Such a situation, however, is far from ideal and a theory that would be able to cover all aspects of pericyclic reactivity by a single unified formalism would be certainly useful and valuable.

In this connection it is therefore interesting that certain progress toward the creation of such a unifying theory has recently arisen from the topological theory of pericyclic reactions based on the so-called overlap determinant method and the least motion principle[14 – 16]. Within the framework of this approach the ease of a reaction is quantitatively characterized by an abstract quantity, the extent of electron reorganization, for the description of which the so-called similarity indices were proposed[17,18]. The broad applicability of these indices for the rationalization of various aspects of pericyclic reactivity was subsequently demonstrated in a number of studies[18 - 20].

Our aim in this study is to follow up with the results of these previous studies, to complement them by a systematic study of substituent effects on various classes of pericyclic reactions and to test the reliability of the proposed model on the basis of comparison of the results with available theoretical and experimental data.

THEORETICAL

Although the detailed formalism of the similarity approach is sufficiently described in previous studies, we consider it convenient to recapitulate briefly the basic ideas of the approach to the extent necessary for the purpose of this study.

The basis of the approach is the so-called generalized overlap determinant method[15,16]. Within the framework of this approach the concerted chemical reaction $R \rightarrow P$ is described by a parametrical transformation formula (*1*), that converts the wave function of the reactant ψ_R into the wave function ψ_P of the product by the continuous variation of a parameter φ.

$$\psi(\varphi) = \frac{1}{N(\varphi)} \left(\cos\varphi \, \psi_R + \sin\varphi \, \psi_P \right)$$

$$\psi_\varepsilon(0, \pi/2) \qquad (1)$$

On the basis of the generalized wave function $\psi(\varphi)$ characterizing the structure of the transient species through which the system passes during its movement along the reaction path, the so-called topological density matrix $\Omega(\varphi)$ is introduced in the second step (Eq. (*2*)).

$$\Omega(\varphi) = N \int \psi(\varphi)^2 \, d\xi_1 \, d\boldsymbol{x}_2 \ldots\ldots d\boldsymbol{x}_N \qquad (2)$$

In terms of this density matrix, the extent of electron reorganization in a given process is characterized by the generalized similarity index $r(\varphi)$ (ref.[17]), which describes, as can be seen from the definition equation (*3*), the similarity of an arbitrary transient structure and the initial reactant.

$$r(\varphi) = \frac{1}{N_{RX(\varphi)}} Tr \, \Omega(0) \, \Omega(\varphi) \qquad (3)$$

Because of normalization, the values of this index are bounded by the inequality $0 < r(\varphi) \leq 1$. This index attains maximum value of unity for $\varphi = 0$, which corresponds to the comparison of the initial reactant with itself, and with increasing φ its values monotonously decreases. When the changes in the values of $r(\varphi)$ caused by the variation of φ are expressed graphically in the form of dependence $r(\varphi)$ vs φ, it is apparent that the extent of electron reorganization in the entire process can be characterized quantitatively by the integral J which characterizes the extent of deviations between the actual $r(\varphi)$ vs φ dependence and a standard line $r(\varphi) = 1$ that corresponds to the hypothetical process where the electron reorganization does not occur at all[17] (Fig. 1). In terms of this index, the problem of substituent affect can be simply investigated on the basis of analysis and interpretation of the changes in the values of J induced by the substitution.

In our case, where the above approach was formulated within the framework of simple HMO method that allows the modelling of the substitution by the change of the Coulombic integral α on the corresponding centers, the whole problem reduces to the determination and interpretation of the dependencies of $J(\alpha)$ vs α. Thus from the above intuitive parallel between the magnitude of J and the extent of electron reorganization, it can be seen that a reaction for which the J values decrease upon substitution can be expected to be accelerated while an increase in J similarly indicates the retarding substituent effect[18].

In the following section the practical use of the proposed approach will be demonstrated by a number of examples of various pericyclic reactions. Since one of the goals of our study is to compare the predictions of our approach with the previous study by Carpenter[21] which deals with the analysis of substituent effect the most systematically, we shall for the most part confine the selection of the pericyclic reactions only to processes analyzed in that study.

RESULTS AND DISCUSSION

Electrolytic Reactions

The simplest representative of this type of reactions is the transformation of butadiene to cyclobutene for which, restricting the discussion to monosubstituted systems only,

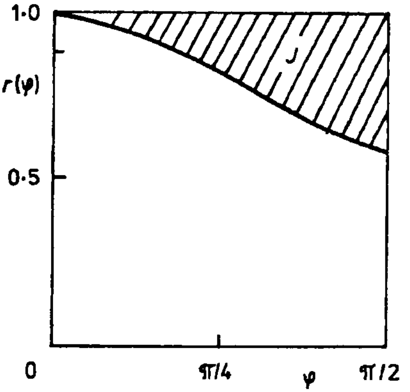


FIG. 1
Schematic visualisation of the extent of electron reorganization measured by the integral similarity index J

two distinct cases that differ in the position of the substitution can generally be distinguished (Scheme 1).

SCHEME 1

Since both these cases were already analyzed in our introductory study[18] it is not necessary to go into details here, and we shall confine ourselves only to a brief recapitulation of the results summarized in Tables I and II.

TABLE I
Calculated values of integral similarity indices J for the allowed and forbidden cyclization of 1-substituted butadienes to corresponding cyclobutenes in dependence on the value of coulombic integral α modelling a substitution

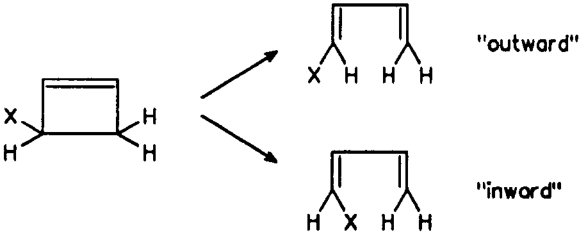
α	$J(\alpha)_{dis}$	$J(\alpha)_{con}$
-3	0.086	0.065
-2	0.112	0.074
-1	0.159	0.087
0	0.195	0.096
1	0.159	0.087
2	0.112	0.074
3	0.086	0.065

TABLE II
Calculated values of integral similarity indices J for the allowed and forbidden cyclization of 2-substituted butadienes to corresponding cyclobutenes in dependence on the value of coulombic integral α modelling a substitution

α	$J(\alpha)_{dis}$	$J(\alpha)_{con}$
-3	0.171	0.110
-2	0.180	0.104
-1	0.190	0.098
0	0.195	0.096
1	0.190	0.098
2	0.180	0.104
3	0.171	0.110

As can be seen from the tables, the allowed conrotatory reaction is predicted to be facilitated by 1- and retarded by 2-substitution, while in the case of disrotatory reaction the effect of both substitutions is facilitating. These predictions are in complete agreement both with the expectations of Carpenter's model[21] and also with available experimental data. This applies especially to all allowed conrotatory cyclizations for which the predicted substituent effect is compatible with the trends in the experimental activation energies[22,23].

In connection with the predicted substituent effect in allowed conrotatory reactions it is also interesting to note that together with the mentioned facilitating effect of 1-substitution, the reaction shows a strong preference for one of the two stereochemically different modes of cyclization[24,25] (Scheme 2).

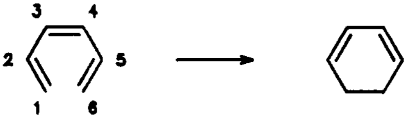


SCHEME 2

Generally it is true that donor substitution prefers the formation of the "outward" type products, whereas for the acceptor substitution the dominant reaction mode leads to the products of the "inward" type. This interesting effect is not, of course, reflected by our simple model, but we are working on a generalization of the whole approach to the level of semiempirical all valence electron methods where, we hope, even these subtler effects will be correctly reproduced.

A slightly more complex situation can be seen in the case of a disrotatory cyclization, for which the forbiddeness of the process strongly reduces the availability of direct experimental data. Even if such scarce data[26] are in agreement with our predictions, a complicating possibility that the reaction does not proceed by a concerted mechanism for which the model is designed cannot be ruled out.

More interesting, however, than the butadiene cyclization is the transformation of 1,3,5-hexatriene to cyclohexadiene. As the discussion is again restricted only to monosubstitution, three different cases can be distinguished (Scheme 3).



SCHEME 3

The most interesting feature of these reactions is that the predictions of our and Carpenter's model in this case differ. Thus e.g. Carpenter predicts the retardation of the reaction by polar substitution for all allowed disrotatory reactions substituted in 1,2 and 3 position. On the other hand, in our case the resulting picture is more complex, and in dependence on the position of the substitution both facilitation and the retardation of the reaction is predicted. The corresponding curves $J(\alpha)$ vs α which reflect this substituent effect are given in Figs 2 – 4.

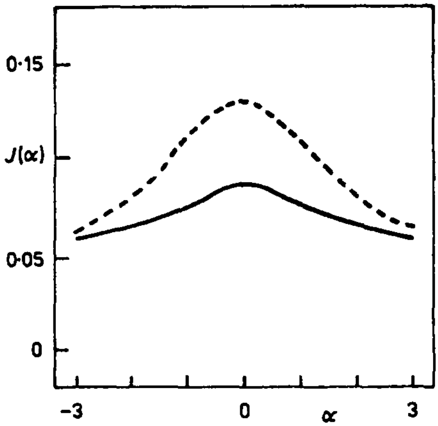


FIG. 2

Calculated dependence of integral similarity index $J(\alpha)$ for the cyclization of 1-substituted hexatrienes to cyclohexadienes on the magnitude of "substituent power" α. (*Full line corresponds to* allowed and broken line to forbidden reaction)

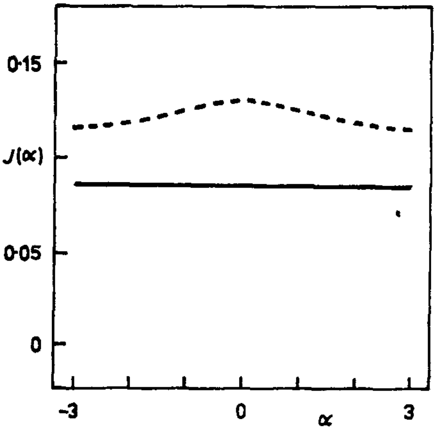


FIG. 3

Calculated dependence of integral similarity index $J(\alpha)$ for the cyclization of 2-substituted hexatrienes to cyclohexadienes on the magnitude of substituent power α. (Full line corresponds to allowed and broken line to forbidden reaction)

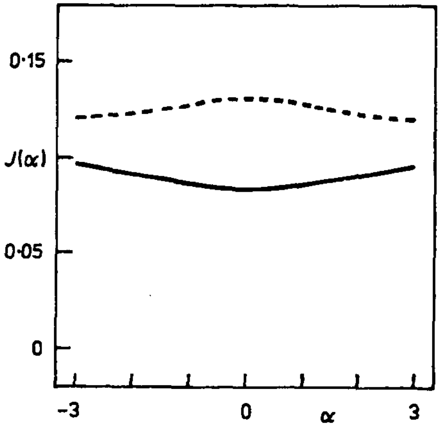


FIG. 4

Calculated dependence of integral similarity index $J(\alpha)$ for the cyclization of 3-substituted hexatrienes to cyclohexadienes on the magnitude of substituent power α. (Full line corresponds to allowed and broken line to forbidden reaction)

From these curves the following conclusions can be deduced: (i) In keeping with the prediction of Carpenter's model, the 3-substitution is predicted to retard the allowed disrotatory reaction. (ii) For the 2-substitution, the sensitivity to substituent effect is much lower and the resulting substituent effect should be practically negligible. (iii) For the 1-substitution, the considerable variance with Carpenter's model is observed and an acceleration of the reaction is predicted.

The best solution of the above discrepancies between the predictions of both models would be, of course, a comparison of the predictions with experiment, but since as far as is known no such data are available, the final decision must remain open. It should be noted, however, that there is a complete parallel of our predicted behaviour with similar conclusions on the closely related system of butadiene to cyclobutene cyclization (retardation of the allowed reaction by substitution on the most remote center).

Cycloaddition Reactions

The simplest representative of this type of reactions is 2 + 2 dimerization of ethene, characterized in the case of monosubstitution by Scheme 4.

SCHEME 4

The reaction can proceed by two alternative mechanisms, the so-called supra–supra and supra–antara additions of which the first is thermally forbidden and the second thermally allowed. The values of corresponding integral indices calculated for both of the above reaction paths by the procedure described in references[15,17] are summarized in Table III.

Let us discuss again the conclusions arising from these values. First of all, it is again possible to see that the values for the allowed $s + a$ addition are generally lower than the ones for the forbidden $s + s$ process. This again confirms that our model correctly reflects the requirements of the least-motion principle, and the extent of electron reorganization in the allowed reaction is lower than in the forbidden one. Concerning the expected substituent effects, the form of both dependencies is very similar, and from the decrease of J with increasing $|\alpha|$ it is possible to expect that both the allowed $s + a$ and the forbidden $s + s$ mechanisms should be accelerated by substitution.

Although this facilitation is indeed observed experimentally, at least for the backward fragmentation of monosubstituted cyclobutanes*, the situation in this case is

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* An exhaustive survey of experimental activation energies can be found in ref.[27].

slightly more complicated since these reactions do not proceed by concerted mechanism from which our predictions are derived, but instead, by a stepwise nonconcerted process via biradical intermediates[28-31]. For that reason it is also difficult to evaluate our theoretical prediction, and no definitive conclusion can be drawn either from it or from the observed disagreement with the predictions of Carpenter's theory. Similarly as in the previous case of hexatriene cyclization it is, however, again interesting, that a certain even if indirect support in favour of our theoretical prediction can nevertheless be found in the 1,3 sigmatropic transformations (Scheme 5), which are topologically equivalent with the above 2 + 2 cycloadditions.

SCHEME 5

In agreement with our theoretical prediction, the allowed *s* + *a* mechanism, which in this case is free of unfavourable steric strain that would prevent the reaction from proceeding concertedly, is indeed facilitated by substitution at the migrating center[32].

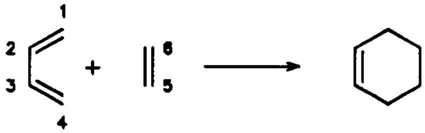
The most typical and the most famous representative of cycloaddition reactions is the Diels–Alder reaction, representing the broad class of 4 + 2 cycloadditions. Because of the immense synthetic importance of these reactions considerable effort in both theory and experiment has been devoted to the reactivity of various substituted systems, and there is therefore a wealth of data with which our predictions can be compared. In the case of experimental studies, however, such a comparison is slightly complicated by the existing uncertainties in the mechanism of these processes[33]. In addition to concerted

TABLE III
Calculated values of integral similarity indices J for the allowed and forbidden ethene dimerization in dependence on the value of the coulombic integral α modelling a substitution

α	$J(\alpha)_{s+s}$	$J(\alpha)_{s+a}$
−3	0.158	0.154
−2	0.168	0.163
−1	0.185	0.176
0	0.195	0.184
1	0.185	0.176
2	0.168	0.163
3	0.158	0.154

mechanism supported by some *ab initio* calculations[34 - 38], an alternative of a nonconcerted mechanism involving the appropriate biradical or zwitterionic intermediates is frequently assumed[39 - 41]. This problem is, however, common to all existing theories of substituent effect on Diels–Alder reactions and none of them is able to resolve the ambiguities with certainty. The maximum we can do is to compare our predictions with the predictions of existing theories based on the similar assumptions[4,5,21].

For simplicity let us begin with the parent Diels–Alder reaction between the butadiene and ethene, and let us discuss the expected response of this system to substitution at positions 1 and/or 6 (Scheme 6). The calculated values of similarity index J are for this case given in Tables IV and V.



SCHEME 6

First what can be seen is that the values corresponding to the allowed $s + s$ reaction are again systematically lower than for the forbidden one so that the qualitative prediction of Woodward–Hoffmann rules is again correctly reproduced. As can be seen, however, from the comparison with the analogous values e.g. in Table I, the difference between the allowed and forbidden reactions is in this case considerably smaller, which thus suggests a closeness in the extent of electron reorganization for both types of reactions. This result is very interesting since just here may lie the origin of a certain delicateness of these reactions, that is reflected in the potential participation of nonconcerted stepwise reaction paths as alternatives not only to forbidden but also to

TABLE IV
Calculated values of integral similarity index J for the parent Diels–Alder reaction in dependence on the coulombic integral α modelling the substitution in position 1

α	$J(\alpha)_{s+s}$	$J(\alpha)_{s+a}$
–3	0.139	0.140
–2	0.145	0.147
–1	0.154	0.158
0	0.160	0.165
1	0.154	0.158
2	0.145	0.147
3	0.139	0.140

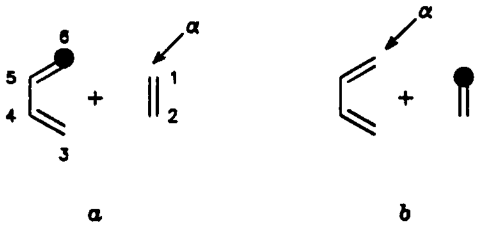
allowed reaction paths. Since, however, our aim is not to discuss the mechanism of Diels–Alder reaction, we leave this problem completely open and instead our attention will be concentrated only to the discussion of substituent effect on concerted reaction mechanism. In this case it is possible to see from the Tables IV and V that the reaction should be generally facilitated both by donor and by acceptor substituents. This result is very interesting since we are again in contradiction with the prediction of Carpenter's model[21]. Although in the similar case of hexatriene cyclization the lack of data prevented us from deciding between both predictions, in this case a decision is possible and this decision is in favour of our model. The reason is that our predictions are in this case in complete agreement with the generally accepted perturbation theory by Sustmann[4,5]. According to this theory Diels–Alder reactions are divided into three classes (neutral, normal and inverse). Our case of parent Diels–Alder reaction characterized in the language of perturbation theory by the simultaneous contributions of both $HOMO_{diene}$–$LUMO_{dienophile}$ and $HOMO_{dienophile}$–$LUMO_{diene}$ interactions represents the neutral system, for which just the acceleration by both donor and acceptor substitution is expected.

After this primary verification of the reliability of our model it is possible to analyze similarly also other types of Diels–Alder systems. The most interesting and also the best experimentally documented in this case is the so-called "normal" reaction, characterized by the dominant role of $HOMO_{diene}$–$LUMO_{dienophile}$ interactions. The shift toward this situation can be induced in the parent system by the introduction of donor substitution into the diene (or the acceptor substitution into dienophile) and the expected response should be the facilitation of the reaction by the acceptor substitution on dienophile (or by a donor substitution on diene). On the contrary, the donor substitution on the dienophile (or the acceptor substitution on the diene) should have the opposite effect. To test this prediction which is in complete harmony with the empirical Alder rules[42,43] we analyzed two model systems formed by: (i) Butadiene modified by

TABLE V
Calculated values of integral similarity index J for the parent Diels–Alder reaction in dependence on the coulombic integral α modelling the substitution in position 6

α	$J(\alpha)_{s+s}$	$J(\alpha)_{s+a}$
−3	0.127	0.128
−2	0.136	0.137
−1	0.150	0.153
0	0.160	0.165
1	0.150	0.153
2	0.136	0.137
3	0.127	0.128

donor substituent $\alpha_D = 1$ in position 1 and ethene substituted in position 6 by a variable substitution changing within the range $\alpha_{\varepsilon}(-3, 3)$. (ii) Ethene modified by acceptor substituent $\alpha_A = -1$ in position 6 and butadiene substituted in position 1 by a variable substituent changing again in the range $\alpha_{\varepsilon}(-3, 3)$ (Scheme 7).



SCHEME 7

The resulting calculated values of corresponding indices, in dependence on the varying substituent power α, are given in Figs 5 and 6. As can be seen from these figures, the predictions of the Alder rules are in both cases confirmed and the same agreement is also observed for the inverse Diels–Alder reactions.

In connection with the above theoretical confirmation of Alder rules it is, however, interesting to note that the predicted retarding effect of electron rich dienophiles (*a* in Scheme 7) or electron deficient dienes (*b* in Scheme 7) is reproduced only for substituents of moderately strong substituent power. For stronger substitutions, corresponding roughly to $|\alpha| > 2$, the resulting curves start to display a tendency toward reversal. This result is very interesting, but since the parametric nature of our HMO

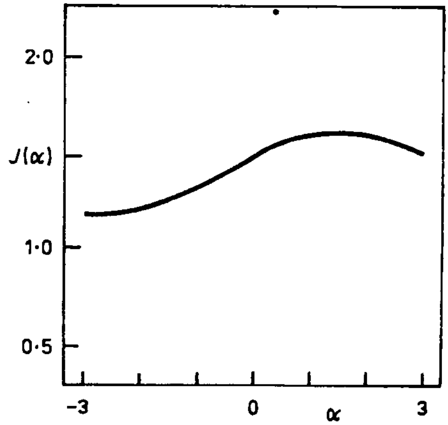


FIG. 5

Calculated dependence of integral similarity index *J* for the allowed Diels–Alder reaction (*7a*) in dependence on the variable substitution modelled by the change of α in the dienophilic component

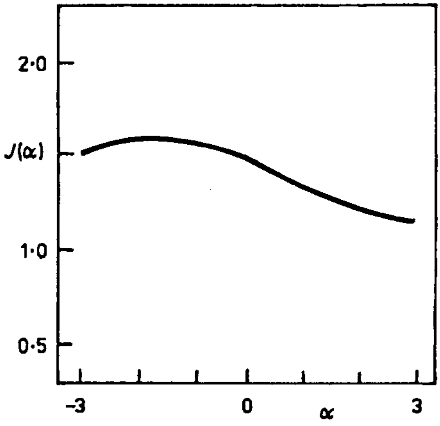


FIG. 6

Calculated dependence of integral similarity index *J* for the allowed Diels–Alder reaction (*7b*) in dependence on the variable substitution modelled by the change of α in the diene component model prevents us from assigning the model α values to specific substituents it is difficult to say where on the real scale of substituents lies the point beyond which the predicted reversal could be observed. For that reason it is also difficult to decide whether the existing data, which seem to suggest no indication of such a reversal, do indeed cover the sufficiently broad range of substituent polarities. Further experimental studies on systems substituted by the sufficiently strong substituents of like polarity are required.

In a completely analogous way it would now be possible to analyze any other reaction. Such analysis need not be restricted to the simplest case of monosubstitution and more complex systems of multiple substitution (where the standard perturbation techniques are difficult to apply*) may be analyzed as well. Summarizing the above results we would like finally to express our belief that the proposed model does provide a new alternative to existing perturbation techniques, in comparison with which it has not only the advantage of conceptual compatibility with the underlying overlap determinant method, but also a greater simplicity and generality owing to which it could be, e.g., incorporated into the programs for computer designed synthesis.

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* In this case the auxiliary concepts of secondary or subjacent orbital interactions are to be frequently invoked[44 - 47].

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