

Similarity approach to chemical reactivity. Torquoselectivity in pericyclic reactions

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The recently proposed topological similarity index was applied to the elucidation of the interesting phenomenon of pericyclic reactivity, the so-called torquoselectivity. It has been shown that the similarity approach is indeed able to provide a simple and consistent explanation of this phenomenon even in nontrivial cases of counter-intuitive contra-steric control.

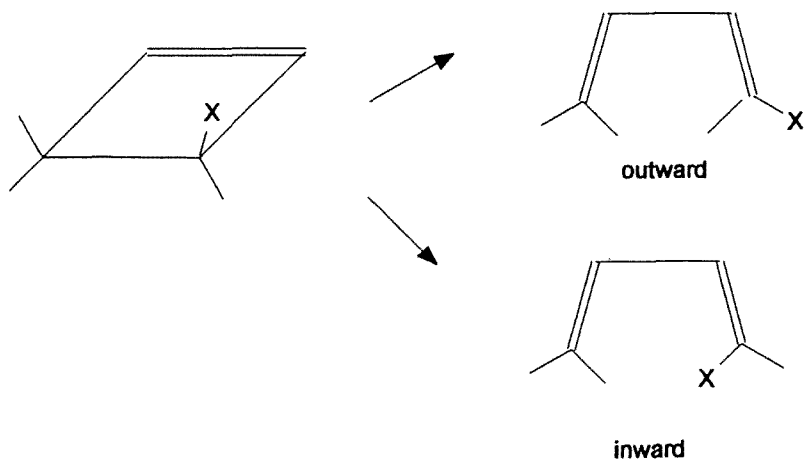
1. Introduction

The study of molecular similarity is one of the most fundamental and rewarding tasks of chemists. Based on similarities, the empirical relations and important rules can be found and new ideas can be inspired, often leading to novel theoretical insights into molecular properties and chemical reactions. Because of the importance which similarity plays in so many different situations, the quantitative study of molecular similarity has experienced major advances in recent years [1–5]. The most relevant for the purpose of this paper are the studies in which the similarity approach was applied to the rationalization of chemical reactivity [6–11]. While the first applications were restricted only to the level of the simple HMO method [9–11], the similarity index, which is the basic quantity in these applications, was recently generalized so as to be applicable to the level of more sophisticated semi-empirical or even ab-initio methods [12]. This generalization considerably broadened the possibilities of the similarity approach, especially in that the emphasis could be shifted from simple model studies to the analysis of real chemical systems. In a previous study [13] we reported the application of this new generalized index to the justification of the so-called Hammond postulate [14]. Our aim in this study is to apply the same index to the rationalization of another interesting phenomenon

of chemical reactivity, the so-called torquoselectivity. This phenomenon was first reported experimentally on a thermally induced conrotatory ring opening of methyl substituted cyclobutenes where the formation of one of the two alternative products (E- vs. Z-substituted butadienes) is preferred over the other [15]. The origin of this phenomenon is the following.

According to Woodward–Hoffmann rules [16], the thermal ring opening of cyclobutene is allowed by the conrotatory mechanism. There are, however, two alternative possibilities of conrotation which differ in the direction of rotation around C–C bonds in cyclobutene (both either clockwise or anticlockwise). In the case of parent unsubstituted cyclobutene these two alternatives are completely equivalent. As a result, the W–H rules speak only of one conrotatory mechanism without specifying the direction of conrotation. This equivalence disappears, however, when substituents are introduced since, as we see from the Scheme I, each of the two alternative directions of conrotation leads to different products. This, of course, suggests that even if both conrotations are allowed by W–H rules, the two alternative rotations may slightly differ energetically so that the preferential formation of one or the other isomer can be expected. Such is indeed the case and the selectivity resulting from these two alternative directions of rotation is known as the torquoselectivity. Since its first discovery on substituted cyclobutenes, the phenomenon of torquoselectivity was found to operate also on other systems [17,18].

The most straightforward approach to the theoretical rationalization of torquoselectivity phenomenon was adopted by Houk [15,19], who calculated the activation energies of individual alternative reaction paths for the ring opening of substituted cyclobutenes with various substituents X. Using this approach he was able to explain not only the preferred formation of E-substituted butadienes in the ring opening of methyl substituted cyclobutenes but also the counter-intuitive contra-steric control of the selectivity in the analogous rearrangement of acceptor sub-



Scheme I.

stituted cyclobutenes [20,21]. Although such a straightforward approach correctly describes the observed selectivities, the complex nature of underlying calculations makes it quite difficult to explain and to understand the origin of the observed phenomena. In order to overcome this drawback, a simple rationalization in terms of orbital interaction rules was proposed by Houk [15,19]. Such an explanation has, however, one disadvantage common to all techniques based on the consideration of certain selected orbitals (like, e.g., the frontier orbital theory [22]). This disadvantage is that its success crucially depends on the selection of interacting orbitals and in the case of "wrong" selection the predictions may fail. For this purpose we decided to reinvestigate the problem of torquoselectivity in terms of the molecular similarity approach, which, because it is based on total densities rather than on individual orbitals, should be free from similar limitations.

Our aim in this study is to demonstrate that the recently proposed similarity approach to chemical reactivity [9–11] is able to provide a simple explanation of the origin of the torquoselectivity phenomenon consistent with the previous orbital interaction rules by Houk.

In this connection, however, it is important to remember that like the orbital interaction rules, the similarity approach is also of empirical nature. This is due to the fact that its validity is derived from another empirical approach, the so-called least motion principle [23,24]. Thus it is not surprising that in order to remain reliable, the similarity approach requires that some additional conditions hold. One of the most important such conditions is that the similarity indices are size dependent so that only the indices derived from the systems of the same size are directly comparable. This seemingly important restriction is not, however, so severe since in our case the similarity indices for the reaction paths leading to isomeric products are compared so that the condition of the size consistency is automatically fulfilled.

2. Theoretical

The basic quantity in our approach is the topological similarity index [25] resulting from the incorporation of the original index by Carbó [26] (eq. (1)) into the framework of Trindle's mapping analysis [27]:

$$r_{AB} = \frac{\int \rho_A(1)\rho_B(1) d\tau_1}{\left[\int \rho_A^2(1) d\tau_1\right]^{1/2} \left[\int \rho_B^2(1) d\tau_1\right]^{1/2}} \quad (1)$$

The index evaluates the similarity of two molecules A, B by comparing the corresponding density matrices ρ_A , ρ_B . In the applications to chemical reactivity the natural choice is to identify the molecules A and B with the reactant(s) and the product(s) of a given reaction. The resulting similarity index r_{RP} is then the basic quantity in terms of which a wealth of various mechanistic problems in pericyclic reactivity could have been explained [9–11]. These applications rely on the interpre-

tation of similarity index [28] as a measure of the extent of electron reorganization required to convert the reactants into the products. Such an interpretation is based on the so-called least-motion principle [23,24], according to which the reacting molecules prefer those reaction paths along which they undergo minimal changes in nuclear and electron configurations. In view of the above interpretation of the similarity index as a measure of the extent of electron reorganization in the process, the ease of a reaction can be characterized by the value of r_{RP} . Generally, it is possible to expect that high values of r_{RP} , indicating low electron reorganization going from R to P, imply an easy reaction while lower values of r_{RP} can be regarded as an indicator of slower reaction.

This intuitive interpretation of similarity indices was practically tested on the alternative reproduction of Woodward–Hoffmann rules [16] and in all cases we found that reactions allowed by these rules generally display higher similarity of R and P than the forbidden ones [25,29,30]. Just the same philosophy of relating the similarity indices to the ease of reaction is also the basis of the present approach to the rationalization of the torquoselectivity phenomenon. Within this approach the ease of two alternative reaction paths leading to two alternative products is estimated by comparing the corresponding similarity indices. In keeping with the general interpretation, the higher values of r_{RP} are expected to indicate an easy reaction and, as it will be shown below, this simple approach is indeed consistent with the observed selectivities.

3. Results and discussion

The above approach was applied to a series of several electrocyclic transformations of substituted cyclobutenes to butadienes. The studied reactions involved:

1. the conrotatory ring opening of 3-substituted cyclobutenes to E- and Z-substituted butadienes,
2. the conrotatory ring opening of 3-methyl, 3-methoxy substituted cyclobutene to corresponding butadienes, and
3. the conrotatory ring opening of perfluoro trans 3, 4 dimethylcyclobutene to the corresponding E, E and Z, Z perfluorosubstituted butadienes.

Each of these reactions will be separately discussed below.

(1) *Conrotatory ring opening of 3-substituted cyclobutenes*

The reaction is schematically described in Scheme I. As we can see, the two alternative reaction paths correspond to “inward” and “outward” rotation. Intuitively one would expect that because of lower steric demands in the product, the outward rotation leading to E-substituted butadienes should be preferred. This is indeed the case for the ring opening of methyl-substituted cyclobutenes but for the acceptor-

substituted systems Houk's rule predicts the contra-steric control to operate. In order to check whether this change of the control of the process will correctly be described by the similarity indices, the similarity approach was applied to the study of the system. This required that first we localize the corresponding reactants and products as the minima on the potential energy hypersurfaces. Based on these structures, the corresponding density matrices ρ_R , ρ_P are calculated and their comparison via eq. (1) leads to the required similarity indices. The calculated values of similarity indices r_{RP_E} , r_{RP_Z} for the reaction paths leading to both alternative reaction products for various substituents X are summarized in Table 1. In the same table, the calculated values of activation energies for the corresponding reaction paths are included for comparison. The calculations were performed by the semi-empirical AM1 method [31] included into the MOPAC package [32].

Let us discuss now the main conclusions suggested by Table 1. The most important in this respect is the fact that for any given X the corresponding similarity indices r_{RP_Z} and r_{RP_E} do indeed differ and this difference is in all cases consistent with the observed selectivity and Houk's rules [15,19]. Thus, in keeping with the expectations, the r_{RP_E} is greater than r_{RP_Z} for electron donating groups whereas for electron accepting BH_2 group the reverse is true, consistent with the preferred formation of Z isomer in this case. We can thus see that the similarity approach correctly predicts the observed selectivity even in the case of counter-intuitive contra-steric control. The fact that this result is not due to simple coincidence can clearly be demonstrated by comparing the similarity indices with the calculated activation energies. As it is possible to see from Table 1, the larger of the similarity indices r_{RP_Z} and r_{RP_E} corresponds, for each X, to the reaction path with lower activation energy. This indicates that the intuitive interpretation of similarity indices as a measure of the ease of reaction is indeed correct.

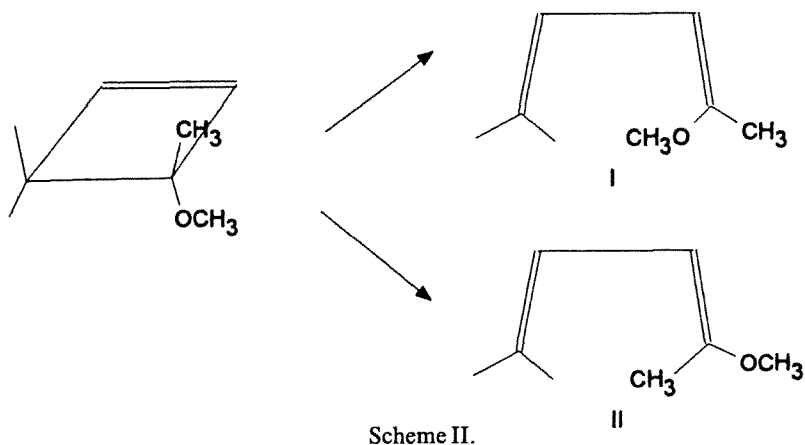
(2) Conrotatory ring opening of 3, 3 disubstituted cyclobutenes

Another interesting example of counter-intuitive control of selectivity in the cyclobutene ring opening was experimentally observed in the rearrangement of 3-

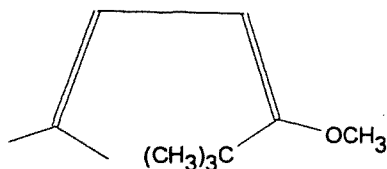
Table 1

AM1 calculated values of similarity indices and activation energies for the alternative reaction paths in the thermally allowed conrotatory ring opening of substituted cyclobutenes.

X	r_{RP_Z}	r_{RP_E}	E_a^Z	E_a^E
H	0.917	0.917	35.4	35.4
F	0.9328	0.9375	36.0	28.0
Cl	0.9275	0.9358	36.9	30.0
Br	0.9251	0.9357	33.5	30.00
OH	0.9298	0.9367	37.4	27.7
Me	0.9259	0.9335	35.3	31.3
BH_2	0.9290	0.9280	26.6	32.0



tert. butyl, 3-methoxy cyclobutene where the more hindered product with E geometry was formed [33].

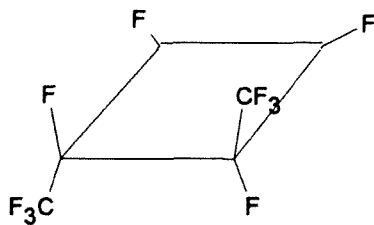


In order to rationalize this result we have performed semiempirical AM1 calculation of similarity indices for the closely related model system of 3-methyl, 3-methoxy cyclobutene (Scheme II).

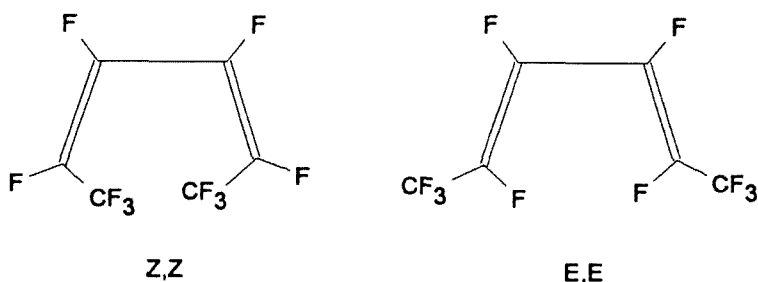
Similarly to the previous cases, both alternative reaction paths which differ in the direction of conrotation and which lead to different products were examined. The similarity indices for both these reaction paths are: $r_{RP_I} = 0.9371$ and $r_{RP_{II}} = 0.9486$. It is nice to see that in keeping with Houk's rules, the larger index corresponds indeed to the preferred reaction for which the methoxy group rotates "outward".

(3) Conrotatory ring opening of perfluoro substituted cyclobutenes

Another example of unexpected contra-steric control of selectivity was experimentally observed for the thermal ring opening of perfluoro trans 3,4 dimethyl cyclobutene [20,21].

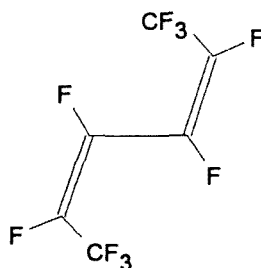


In the original study [20] the authors claimed that consistent with Houk's rules, the electron accepting CF_3 groups preferentially induce the "inward" rotation leading to the formation of *Z,Z* disubstituted product.



In order to test the reliability of Houk's rules in this case we calculated the similarity indices between the starting reactant and both *Z,Z* and *E,E* products and these values are summarized in Table 2.

We see that these indices are not consistent with the observed stereochemistry. A possible explanation for this discrepancy came from a more recent experimental study [35] in which the configuration of the prevailing product was reinvestigated. It was shown that the *Z,Z* configuration is indeed preferred in the product, but the product has a trans rather than cis configuration of the butadiene skeleton.



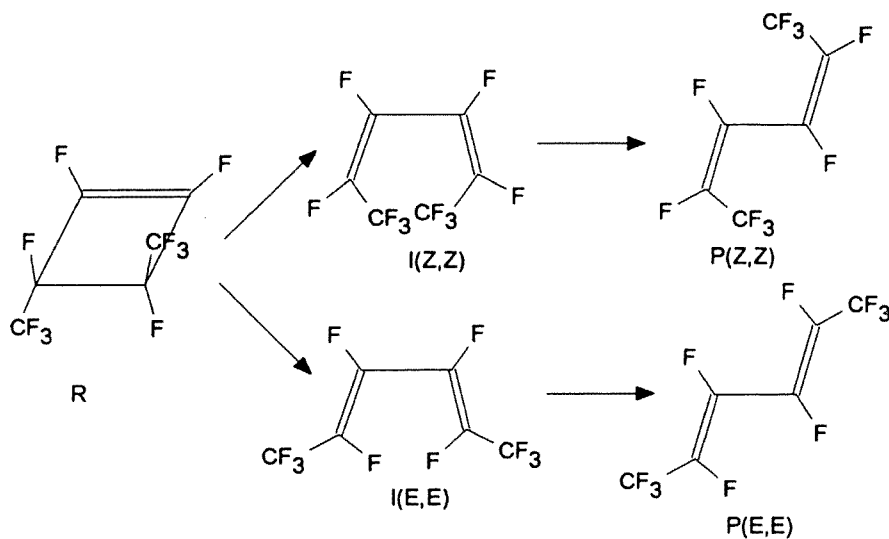
This seems to suggest that the reaction proceeds as a two-step process of which the first step consists of a "normal" conrotatory ring opening which yields the primary product with the *cis* configuration of butadiene skeleton. This primary product then undergoes, in the second step, the *cis-trans* isomerization leading to the final products (Scheme III).

Let us accept now this two-step mechanism of the process and let us apply the similarity approach to it to determine its stereochemical consequences. The metho-

Table 2

AM1 calculated values of similarity indices for "inward" and "outward" conrotatory ring opening of perfluoro *trans* 3,4 dimethyl cyclobutene.

$r_{\text{RP}(\text{Z,Z})}$	$r_{\text{RP}(\text{E,E})}$
0.9727	0.9789



Scheme III.

dology of the application of the similarity approach to two-step reaction schemes was developed in our previous study [34] and so only a brief account of its basic conclusions is given here. The basic idea is to characterize the extent of electron reorganization of the two-step process (2):



in terms of quantities describing the electron reorganization in individual steps. Within similarity approach these quantities are the similarity indices r_{RI} and r_{IP} and as it was demonstrated in [34], the overall extent of electron reorganization in the whole process is then given by the product $r_{RI}r_{IP}$. Applied to our problem, the relative ease of the formation of Z,Z and E,E final trans butadienes can be estimated by comparing the product $r_{RI(Z,Z)}r_{I(Z,Z)P}$ with the product $r_{RI(E,E)}r_{I(E,E)P}$. The calculations were again performed by the semiempirical AM1 method and the resulting similarity indices are summarized in Table 3.

As we can see, the value of the product corresponding to the more favourable reaction path is indeed higher than for the alternative path so that the original discrepancies are simply remedied by the two-step process.

In addition to this reproduction of experimental results, which was the main goal of the above analysis, there is yet another interesting aspect that can be deduced from the values of similarity indices. This concerns, above all, the comparison of the values $r_{RI(Z,Z)}$ and $r_{RI(E,E)}$, which describe the relative ease of the first step of the process, with the values for the whole two-step process.

The reversal of the originally wrong prediction, based on the indices for cis butadienes, arises from the fact that the index $r_{I(Z,Z)P}$ is very close to unity while the other

Table 3
AM1 calculated values of similarity indices for the process described by Scheme III.

Product configuration (direction of conrotation)	r_{RI}	r_{IP}	r_{RIIP}
Z,Z ("inward")	0.9727	0.9986	0.9716
E,E ("outward")	0.9789	0.9721	0.9516

one is much lower. The high value of $r_{I(Z,Z)P}$ can very simply be understood by looking at the structures of the primary cis and trans isomerized Z,Z product. As we expect, the huge steric strain in the Z,Z primary product will certainly prevent the cis butadiene skeleton to be planar and, according to AM1 calculations the actual value of the CCCC dihedral angle is as large as 114° . If we compare this value with the value 141° for the final Z,Z product, it is possible to see that both structures are already very close. This implies that very small structural reorganization is in fact required for the last isomerization step of the process, consistent with the high value of the similarity index. We can thus see that the similarity approach successfully explained even this nontrivial example of contra-steric control of the conrotatory ring opening.

In view of this results and if we take into account a wealth of previous successful applications of similarity indices in other areas of pericyclic reactivity, it is perhaps justifiable to express our belief that the systematic application of these indices may become a new, well-documented approach to the theoretical study of structure-activity relationships.

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