

Multidimensional explorations into chemical reactivity: the reactivity space

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This paper discusses the empirical methods we developed for quantifying electronic and thermochemical effects in organic molecules. The parameters thus calculated can be used as coordinates of a space; points in that space represent the breaking of bonds. The study of such spaces by computer graphics provides important insights into the driving forces of chemical reactions and can help in elucidating reaction mechanisms.

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In the last several decades, calculations of the structure, energy and various physical properties of molecular species by quantum mechanical methods have progressed rapidly. However, obtaining data on the reactivity of molecules by theoretical methods is tedious and time-consuming.

We were faced with the task of having to make predictions on the reactivity of a wide variety of organic compounds in the development of EROS (elaboration of reactions for organic synthesis), a program system for predicting chemical reactions and the design of organic syntheses.¹ In a typical study with EROS, several hundred molecules with 50 to 70 atoms have to be considered, and predictions have to be made on the course of their reactions. We rejected a quantum mechanical approach to solve that problem in a general manner because it was unfeasible for our resources. Nevertheless, we wanted to base our predictions on quantitative evaluations to be able to handle problems of multisite reactivity, regioselectivity, side reactions and protection of functional groups.

In our strategy to solve the problem of making decisions on the course of chemical reactions, we were guided

by the approach taken by an organic chemist. The chemist tries to develop the mechanism of a reaction to rationalize or prognosticate the direction and products of a reaction. In doing so, he or she uses physicochemical concepts like charge distribution, inductive, resonance, polarizability, or steric effect and bond dissociation energy. To a large extent, knowledge on these effects is only qualitative, or semiquantitative at best.

We believed that quantifying these chemical effects could offer new possibilities for furthering the understanding of chemical reactivity. In order to be able to make calculations on fairly large molecules and to study big data sets, procedures were developed that are characterized by short computation times. These methods are all empirical in nature and are briefly summarized in the next section.

One of the most difficult aspects of predicting chemical reactivity is that chemical reactions are usually simultaneously influenced by several effects. The extent to which these effects contribute to chemical reactivity varies from reaction to reaction. In other words, chemical reactivity is a multivariate property. Multivariate problems can be studied in multidimensional spaces. This idea led to the definition of reactivity spaces, spaces that have the various chemical effects as coordinates and allow the study of chemical reactivity (section 2).

THE COORDINATES: CHEMICAL EFFECTS

Partial atomic charges

The sigma-charge distribution was calculated by iterative partial equalization of orbital electronegativity (PEOE).² This method provides values for partial charges and residual electronegativity for each atom in a molecule reflecting both the type of an atom and its molecular environment. In addition, the charge shifted across each bond of a molecule during the iteration process is calculated. This value Q_{sig} is a good measure of the polarity of a bond. The pi-charge distribution was obtained from a method that generates all resonance

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structures of a molecule and weights them according to the potential of the sigma-charges and topological criteria.³

Inductive effect

The values of the residual sigma-electronegativities obtained from the PEOE method can be used as a good measure of the inductive effect.⁴

Resonance effect

In the studies dealt with here, stabilizing formal unit positive and negative charges obtained by polar breaking of bonds is an important factor. The stabilization of these charges by the resonance effect is calculated by a method similar to the procedure for determining pi-charge distribution. All possible structures for delocalizing the formal charges are generated and weighted based on pi-electronegativity values. These calculations also consider the contribution of β -CH and β -CC bonds to stabilizing positive charges (i.e., the hyperconjugation effect is included in this parameter).

Polarizability effect

A procedure had been given for the calculation of an effective polarizability on each atom of a molecule.⁵ The total number of electrons in a molecule used in the equation of this method has the effect that atoms more than four bonds away become unduly handled. Absorbing the number of electrons in the increments of the atom through reparameterization solved that problem.⁶ Apart from the deficiency of the former method for the influence of atoms many bonds away, the values of the two methods are very similar.

Bond dissociation energies

Heats of reaction can be effectively calculated by an additivity scheme.⁷ By including parameters for radicals, access can be gained to bond dissociation energies.

Parameters

For each bond of a molecule we calculated the following parameters by the above procedures:

- bond polarity (Q_{sig})
- difference in pi-charges on the atoms of a bond (Δq_π)
- difference in total charges on the atoms (Δq_{tot})
- difference in residual sigma-electronegativity of the two atoms (X_{sig})
- sum of the resonance effects for stabilizing the positive and negative charges generated by polar breaking of the bond (R)
- sum of the effective polarizabilities of the two atoms (α_b)
- bond dissociation energy (BDE)

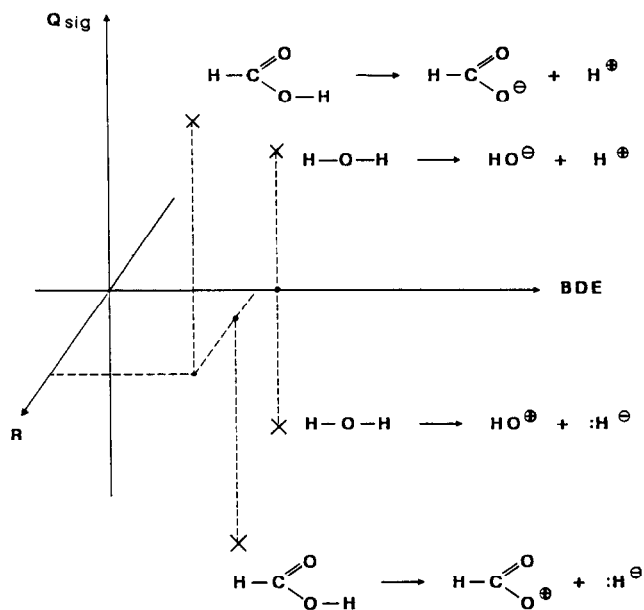


Figure 1. Reactivity space showing the two conceivable ways of heterolysis of the OH bond in water and in formic acid. BDE = bond dissociation energy (in kcal/mol); Q_{sig} = sigma-bond polarity (in electron units); R = amount of resonance stabilization of charges

THE SPACE: POLAR REACTIVITY

The above parameters can be used as coordinates for defining spaces. We call these spaces reactivity spaces, because they are used for studying problems of chemical reactivity. A bond can be represented by a point in such a space, its coordinates being determined by the specific values of the various parameters for this bond.

When dealing with the polar breaking of a bond, a bond will be characterized by *two* points representing the two choices for assigning the positive and negative charge to the two atoms of the bond. This is illustrated in Figure 1 for a reactivity space that has bond dissociation energy, bond polarity, and resonance effect as coordinates. The OH-bond of water and of formic acid each have two choices for heterolysis, and therefore each is represented by two points.

In breaking the OH-bond of water, the electron pair can either be shifted to the oxygen — a direction that is already reflected in the polarity of the OH-bond — or formally break against that polarity giving OH^+ and H^- . There is no possibility of stabilizing charges by resonance on OH^- and H^+ , or OH^+ and H^- ; therefore, the coordinate for R is zero in both cases.

The two conceivable ways of breaking the OH-bond in formic acid give ions that can be stabilized by resonance. In this case, resonance stabilization of the negative formate ion is much larger than in the positive ion. Note that the points for the two much less likely ways of breaking the OH-bonds in water and formic acid by shifting the electron pair to hydrogen are found in the lower part of the space of Figure 1, whereas the preferred heterolyses are in the upper half of this

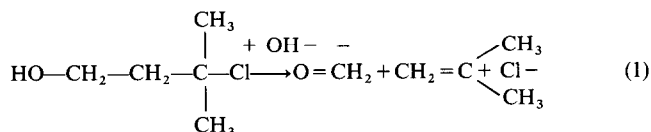
reactivity space. Thus, likely and unlikely heterolyses of bonds are well separated.

We have performed extensive studies of reactivity spaces containing points for the bonds of a wide range of organic compounds. Several statistical and pattern-recognition methods have been used to analyze such spaces as an inroad to a quantification of chemical reactivity.⁸ In fact, mathematical functions have been developed that enable us to calculate the reactivity of aliphatic single bonds, multiple bonds, and bonds in aromatic systems. Based on these reactivity values, the course of the complex organic reactions can be predicted.¹

The purpose of this paper is to show that reactivity spaces can also be analyzed in a less abstract manner. This can be accomplished by computer graphics techniques. These studies pictorially support and supplement our statistical calculations.

Statistical methods allow the study of spaces with many dimensions, even those that are too high for graphical representation. Thus, we have routinely worked with six- and seven-dimensional reactivity spaces. However, these studies have shown that the information contents of these spaces can, in many cases, be represented without much loss of information in three-dimensional (3D) spaces. Under these circumstances, projections of 3D reactivity spaces onto the two dimensions of a graphics screen are a good representation of the reactivity information.

The equation below investigates the reactivity of 3-chloro-3-methyl-1-butanol (1). We chose this example because its course cannot be explained from simple considerations of the reactivity of the functional groups in this molecule. Under basic conditions, a fragmentation reaction occurs with the breaking of a CC-single bond, as seen below.



This points to a breakdown of the concept of functional groups, for within that concept, CC-single bonds are not considered as reactive bonds. Understanding the fragmentation reaction asks for a modeling of the individual steps of the reaction mechanism. This is where considerations on the importance of the various chemical effects have to be made. An outline of how this reaction and some potential side reactions are handled by EROS has already been given.⁹ Therefore, the study here can explain some of the foundations of EROS.

THE TOOL: COMPUTER GRAPHICS

We performed all calculations and displays on a Sun 3/160C workstation. For each bond of a molecule, we calculated the seven parameters mentioned in the first section and stored the results in a data matrix. The user has the option of assigning the bonds to various categories. Various conceivable ways for the polar

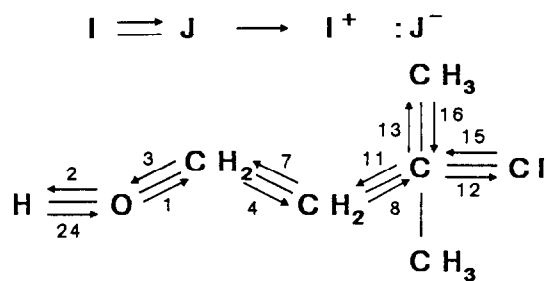


Figure 2. Numbering of some conceivable ways for the polar breaking of various bonds in 3-chloro-3-methyl-1-butanol. The arrow at a bond indicates the shift of the electron pair on heterolysis

breaking of bonds in 3-chloro-3-methyl-1-butanol are indicated in Figure 2 and are given numbers.

These bond breakings have been assigned to groups of reactive, nonreactive and uncommitted bonds. Furthermore, users can select from the seven parameters those three that they want to be taken as coordinates of a reactivity space.

Figure 3 shows the bond breakings of Figure 2 in a reactivity space spanned by the resonance effect (R), bond dissociation energy (BDE) and sigma-bond polarity (Q_{sig}). (In the bonds considered here, the only contribution to the resonance effect comes from hyperconjugation.) The assignment of the C-Cl, H-O, and C-O bond as potentially reactive (cubes) will be generally agreed upon, as will be the choices for the nonreactive bonds (pyramids). An important aspect of this picture is that the reactive bonds are clearly separated from the other bonds. This indicates that the property that is being investigated, chemical reactivity, is well represented in this 3D space.

Figure 4 again shows the heterolyses of Figure 2 now in a space defined by sigma-bond polarity (Q_{sig}), resonance effect (R), and the difference in residual sigma-electronegativity (X_{sig}) of the atoms of the bond considered. This space and the projection selected here emphasize particularly well the good separation of the reactive bonds.

We have drawn several conclusions from Figures 3 and 4. Reactive bonds clearly separate from the other bonds and are distinguished by large positive sigma-bond polarities (the direction of shifting the electron pair coincides with the polarity) and negative electronegativity differences (the electron pair is shifted to the atom with the higher electronegativity). The magnitude of the bond dissociation energy is apparently not important here, since the reactive bonds can also have rather large BDEs. The unimportance of BDE underscores the overriding influence of the solvent on polar reactivity. The resonance (or hyperconjugation) effect does not necessarily have to assume large values to cause initial bond breaking in 1. Overall, in neutral 1 the bond polarity is the most important influence on reactivity.

In Figures 3 and 4, 3D spaces have been studied as projections onto two dimensions. Use of different symbols for different types of bonds allowed further distinction. However, if both different bonds and different molecules are to be compared, an additional

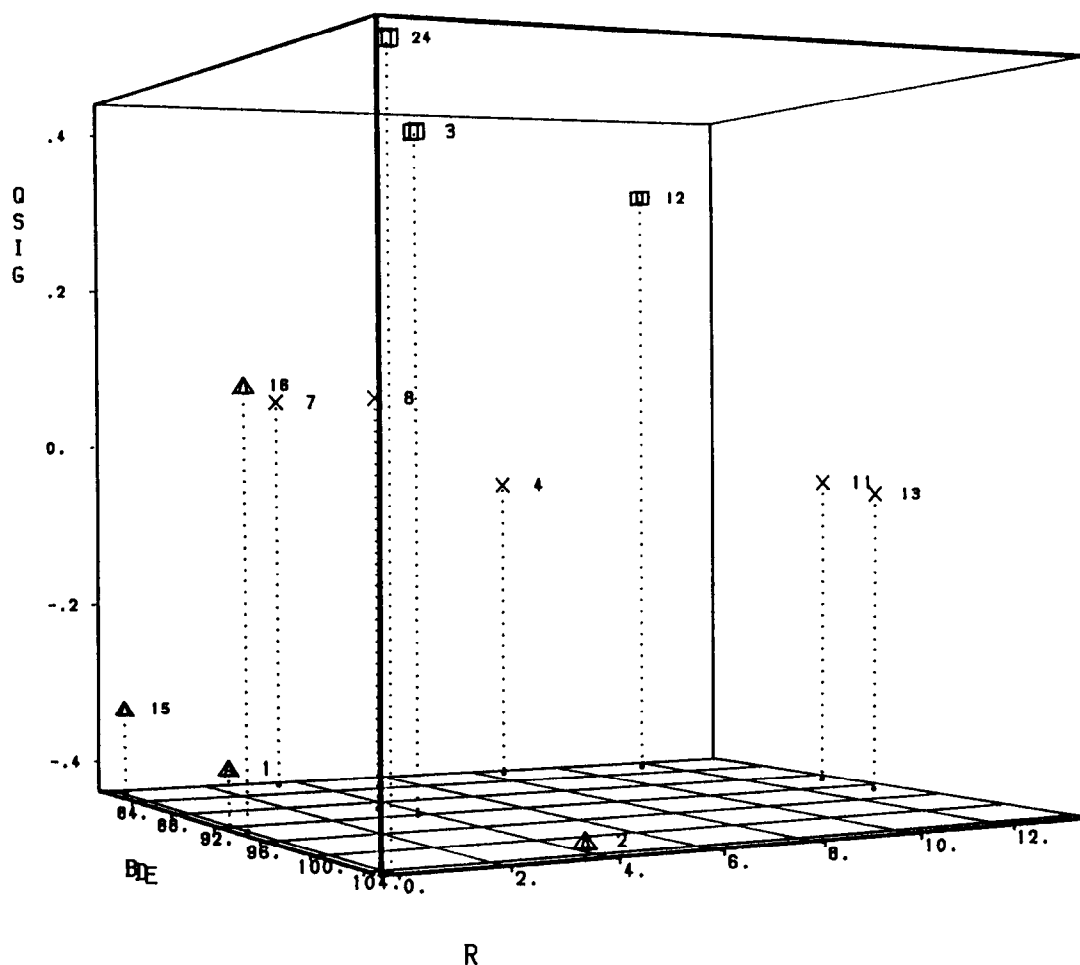


Figure 3. Reactivity space for the bond breakings in 1 of Figure 2. Nonreactive bonds are shown as pyramids, reactive bonds as cubes, uncommitted bonds as crosses. R = resonance effect; BDE = bond dissociation energy (in kcal/mol); Q_{sig} = sigma-bond polarity (in electron units)

dimension is needed. This is where color comes into play.

Figure 5 gives the numbering for various heterolyses of bonds in 3-chloro-1-propanol, 2, which is the demethyl (nor) compound of 1.

In Color Plate 1, the polar breaking of bonds in 1 (yellow) is compared with those of corresponding ones in the primary alcohol 2 (purple). The largest differences are observed for the heterolyses 11 and 12, both being distinguished in 1 by a much higher value of R due to the hyperconjugation effect of two methyl groups on an incipient positive charge on C-3. All the other mutually corresponding bond breakings in the two compounds are characterized by points that lie close together, showing their closely related reactivity.

To develop the individual steps of the reaction mechanism for the fragmentation of 1 (equation 1), two of the three reactive bonds in 1 have been broken; the C-Cl bond (point 12) and the H-O bond (point 24). Then, again all chemical effects have been calculated for the two ions 3 and 4 that are thus formed (Figure 6). The reactivity of various bonds in 3 and 4 is compared with the reactivity of the corresponding bonds in 1 in Color Plate 2.

The bond breakings in the three different chemical species are distinguished by different colors: 1 (white), 3 (blue), 4 (yellow). Selected bonds in these structures are highlighted in red for further discussion. Loss of a chloride ion does not substantially increase the reactivity of the H-O bond, for points 24 (of 1) and 22 (of 4) lie on top of each other. However, it should be pointed out that this conclusion was only drawn from a consideration of the three chemical effects used as coordinates in Color Plate 2. Using other coordinates might change that picture.

Of particular interest is the reactivity of the C(1)-C(2) single bond, a cornerstone in the fragmentation reaction. This bond has the number 4 in 1, the number 3 in 3 and again number 4 in 4. The 3D space shows that the reactivity of this bond is not changed very much after deprotonation of 1 to give 3, as point 4 and point 3 are lying close together. On the other hand, by loss of the chloride anion, to give 4, the resonance effect increases drastically when breaking that CC single bond (bond 4 in 4 is the clearly separated red point 4). Thus, loss of the chloride ion is a major driving factor of the fragmentation reaction.

The message to be drawn from Color Plate 2 is that

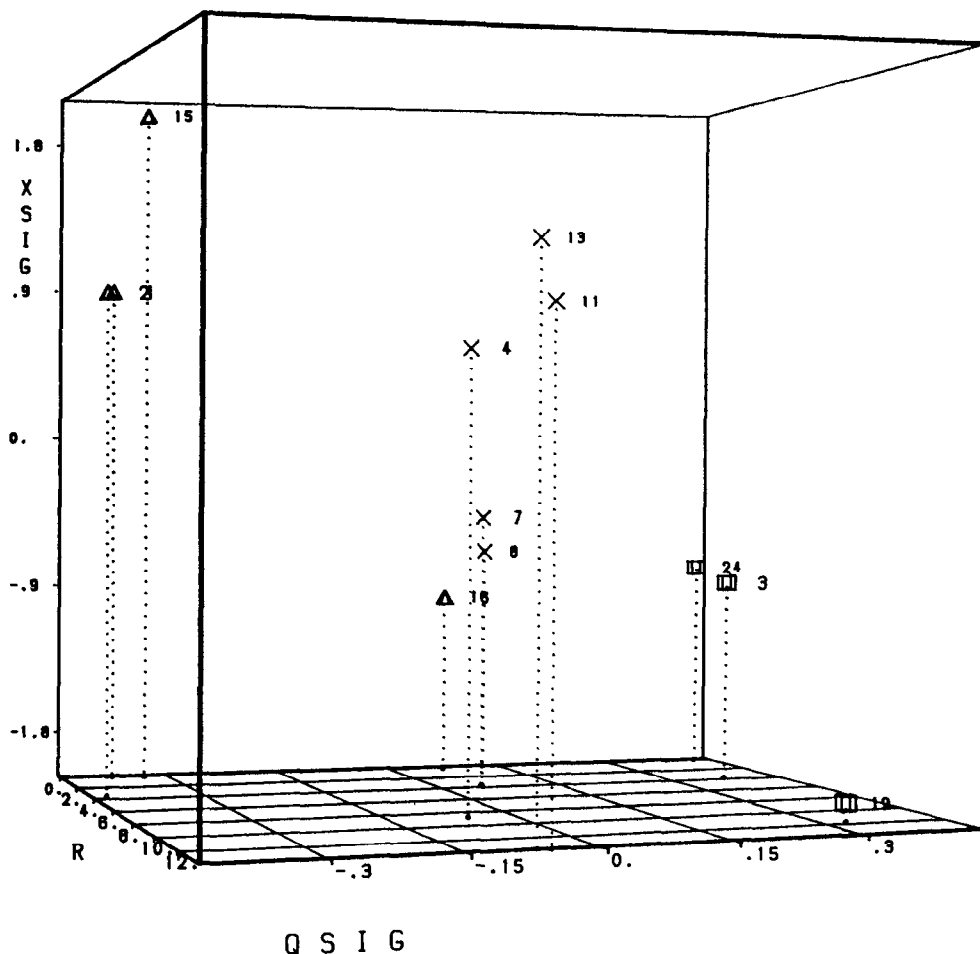


Figure 4. Reactivity space for the bond breakings in 1 of Figure 2. X_{sig} = difference in residual sigma-electronegativity (in eV)

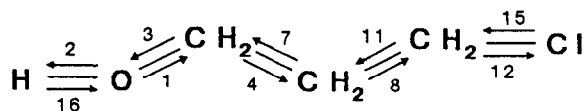


Figure 5. Numbering of conceivable polar breaking of bonds in 3-chloro-1-propanol, 2, significance of arrow as in Figure 2

the reactivity of the CC bond is not greatly enhanced in the anion 3. This CC bond will break only when the chloride ion is simultaneously lost. This suggests that after deprotonation to 3 the two bond breakings in the fragmentation reaction (C-C and C-Cl) occur in a concerted manner.

Color Plate 2 shows that the reactivity of the C-C bond (point 4) is markedly enhanced in 4. Therefore, this bond was broken to further explore possible reaction mechanisms in this system. Calculations were performed on the species 5 and 6 (Figure 6) and their reactivity was compared with that of 4 and 1 in Color Plate 3.

Again, the reactivity of the CC bond is represented by the two red diamonds having number 4. The reactivity of the HO-bond is rather similar in 1 and 4 as already observed in Color Plate 2 (points 24 and 22, marked red, are on top of each other). However, after breaking

the CC bond, the reactivity of the HO-bond (point 6 in red in Color Plate 3) increases substantially as the resonance effect of the carbocation to stabilize the negative charge on oxygen (by forming a CO-double bond to give formaldehyde) attains a rather large value. From this the conclusions can be drawn that by starting to break the CC-bond in 4 the HO-bond might break simultaneously. In other words, after dissociation of a chloride anion from 1 to 4 (e.g., by treatment with Lewis acids like silver ion), a fragmentation reaction could also be expected.

EXPERT KNOWLEDGE

The definition of the chemical effects used in the discussion of the reaction mechanism is built on a vast amount of observations. Thus, these effects encompass the knowledge of the chemist-expert. Many of these factors have now been quantified.

With computer graphics techniques, the important influences of these effects on chemical reactivity can be deciphered. The conclusions thus drawn can be built as rules into an expert system for the prediction of the course of chemical reactions. Planes of separation of reactive from nonreactive bonds can be put into the

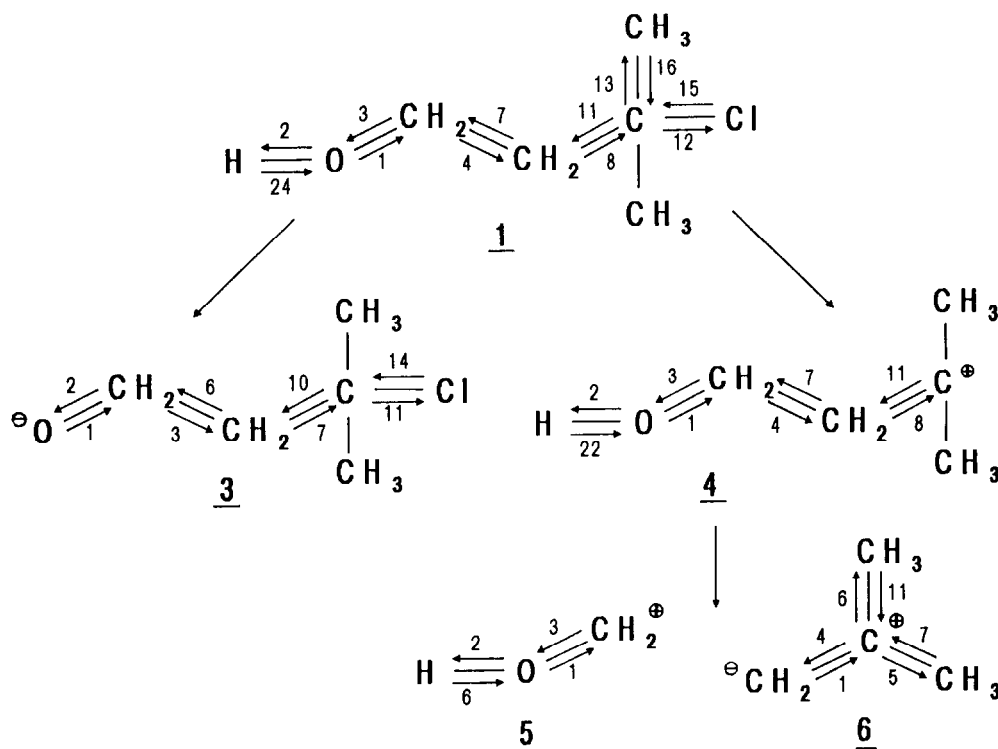


Figure 6. Intermediates in the reaction of 2 showing the numbering for the bond breakings

reactivity spaces by inspection. In this way, boundary values can be given and the rules on the importance of the various chemical effects can even be quantified.

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