Dynamic modeling of chemical reactions: the Diels-Alder cycloaddition

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In order to visualize the stereochemical aspects of the Diels-Alder model cycloaddition of ethylene on butadiene, we developed a computer graphics animated model. The structural data base was deduced from MINDO/3 calculations, and the application program makes it possible to display in detail the different steps of the reaction mechanism. The scope of the application has been enlarged by a similar representation of the Diels-Alder cycloaddition of bis(methylene)-2,3 bicyclo[2.2.1]heptane to ethylene. Both of these examples suggest that molecular graphics is an ideal tool for visualizing and understanding the stereochemistry of complex chemical reactions.

Molecular graphics is now a popular tool in chemistry.[1] Numerous applications range from the design of new drugs[2] to the planning of novel pathways in organic synthesis.[3] Though the major developments in molecular graphics have taken place so far in up-to-date applications of computer-assisted chemistry in both fundamental and applied research, several spectacular achievements have also been made in chemical education.[4] Indeed, computer graphics is an ideal tool for teaching stereochemistry, i.e., the 3D architecture of molecules and its chemical consequences, or for illustrating the detailed mechanistic aspects of chemical reactions. In the latter case, by means of dynamical simulation techniques, a real-time graphic animation of the reacting chemical structures is performed, using the techniques we have previously described for unimolecular rearrangements and vibrations.[5,6]

In this paper, we describe an application we recently developed in order to display on a raster system a real-time animation of biomolecular reactions of Diels-Alder type: (1) the cycloaddition of ethylene on butadiene, a basic reaction of organic chemistry; and (2) the cycloaddition of bis(methylene)-2,3 bicyclo[2.2.1]-heptane to ethylene, which has been studied recently in our laboratories.[7]
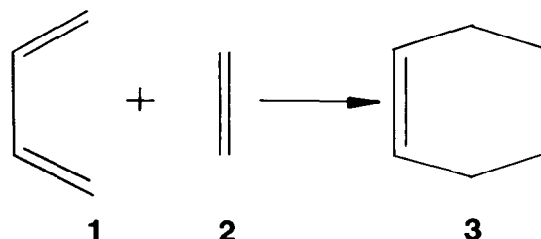
METHODS

The reaction of s-*cis*-butadiene and ethylene is a classical, model example of the Diels-Alder reaction ([4 + 2] cycloaddition).

Scheme 1

In this scheme, compounds *1* (s-*cis*-butadiene) and *2* (ethylene) are the reactants, whereas *3* (cyclohexene) is the product of the reaction. In addition to presenting an adequate pathway for the approach of *1* and *2*, leading finally to *3*, the simulation should describe the important geometrical distortions of *1* and *2*, which occur while the reaction takes place. Actually, as previously reported,[5] the computer graphics simulation of such chemical reactions is an elaborate task that can be divided into two parts. The first involves the calculation of a data base, made of molecular geometries and corresponding energies, which makes it possible to connect the reactants and the product on the energy profile (Figure 1). This is usually performed using a quantum chemistry or molecular mechanics model. The second part involves the conception and realization of the dynamical computer graphics application; a smooth reaction path is obtained by consecutive interpolations within the points of the data base, which makes it possible to visualize the different steps of the approach of *2* toward *1*, leading gradually to the transition state (Figure 1) and finally to the product *3*.

In this application, we decided to place emphasis on the considerable potential of molecular graphics for visualizing and understanding reaction mechanisms, and not on performing expensive, state-of-the-art calculations so as to obtain a structural data base of the highest quality. The data base has therefore been calcu-
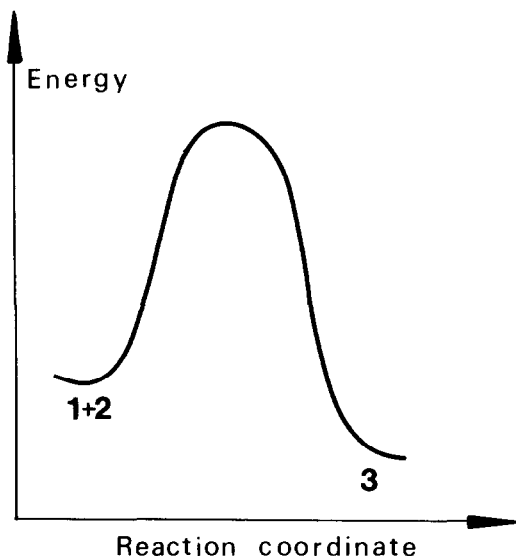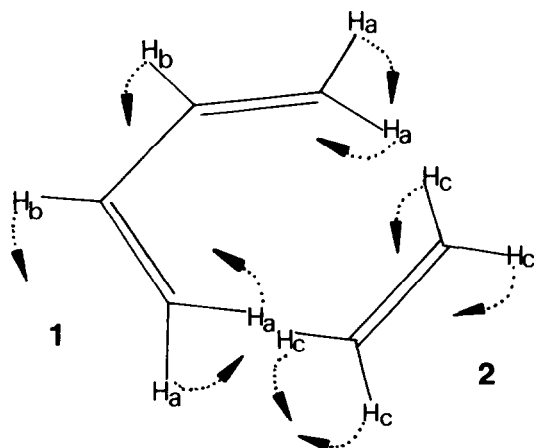

Scheme 1

Figure 1. Qualitative energy profile of the reaction 1 + 2 → 3

lated by semiempirical MINDO/3 method by using the procedure of inverse reaction path: starting from the boat conformation in the cyclohexene adduct, the two allylic C-C σ bonds have been simultaneously elongated conserving the C_s symmetry, which leads to a model for the concerted reaction. Indeed, this model is supported by several quantum chemical calculations.[8] However, Diels-Alder reactions involving nonsymmetrical reactants might proceed via asynchronous formation of σ bonds.

As an example, the data base calculated along the reaction path *1 + 2 → 3* (Figure 1) is made of 15 sets of *1 + 2* (or *3*) structures, obtained by full geometry optimization of reactants and product. The structures exhibit important intramolecular distortions of hydrogen atoms, which are usually neglected in standard descriptions of the reaction.[9]

Scheme 2

In this scheme, seven intermediate points have been obtained by linear interpolation between two consecutive steps of the data base, which leads to 113 images to be displayed one after another on a frame buffer system GDP 500. This raster scan color display of 512 × 512 pixels is linked to a PDP-11/60 host computer. The

Scheme 2

successive geometries of the reaction path are first loaded into the core of the frame buffer and then displayed by means of a high-speed raster converter, which allows for real-time animation. The structure of the application program, which is written in FORTRAN, is presented elsewhere.[10]

RESULTS AND DISCUSSION

This application is intended primarily for a detailed presentation of the stereochemistry of Diels-Alder cycloadditions. The first part, mostly devoted to students, represents the different steps of the prototype reaction of butadiene with ethylene to form cyclohexene. In an attempt to enlarge the scope of the application, a case of more elaborate Diels-Alder cycloaddition, namely that of bis(methylene)-2,3 bicyclo[2.2.1]heptane to ethylene,[7] has been treated using the same dynamic modeling procedure. In our opinion, such applications should be used both for teaching reaction mechanisms and for presenting results in physical organic chemistry.

Before this reaction can actually take place, butadiene must undergo an internal rotation around the single C-C bond. Indeed, because of steric interactions, the s-*trans* conformation is more stable than the s-*cis* rotamer, which is the reactive conformation in the Diels-Alder addition. Color Plate 1 represents different steps of the rotation of the double bonds of butadiene around the single C-C bond so as to give the s-*cis* conformation. To display a smooth process, a series of intermediate conformations have been calculated by varying the $C=C-C=C$ dihedral angle by steps of 2.5°. A series of successive conformers is displayed in Color Plate 1b.

We can now proceed to the reaction of cycloaddition itself, which has been modelized using the method described in the previous section. Note that the reaction occurs in the suprafacial mode, that is, the diene (s-*cis*-butadiene) exhibits to the attacking dienophile (ethylene) the same face throughout the process. Color Plate 2 shows the reactants, the product, the transition state and some intermediate structures as well. It is immediately clear that the hydrogen atoms attached to central carbon atoms of butadiene do not remain within the molecular plane during the reaction as they bend toward the attacking dienophile (Color Plates 2b–2e). Simultaneously, distortions are observed on the terminal C-H bonds of the diene and on those of the dienophile as well. For didactic purposes, the reaction can be stopped at any stage in order to visualize in detail the stereochemistry of the reactants. In addition, it is possible to display also the inverse reaction, the so-called retro-Diels-Alder cycloreversion.

At the final stage of the reaction, the cyclohexene molecule exhibits boat conformation *3a*. However, this conformation is less stable than the half-chair *3b* which is preferentially adopted by the molecule.

Scheme 3

Another sequence was desiged to dynamically represent the interconversion path *3a → 3b*. To this end, the procedure is analogous to that followed for the cycloaddition itself; the animated sequence is made of 73 frames spaced out along the reaction path (Color Plate 3). Actually, from a purely chemical point of view, the
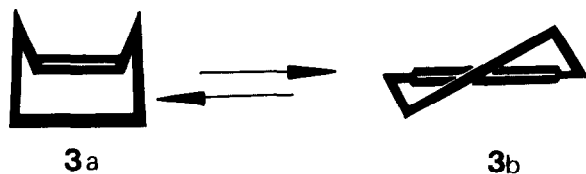
3a   **3b**

Scheme 3

decomposition of the reaction $1 + 2 \rightarrow 3b$ into separate processes $1 + 2 \rightarrow 3a$ and $3a => 3b$ is artificial, since there is no doubt that they overlap somewhat in time. However, this procedure has the advantage of being simpler from a pedagogical point of view.

Let us turn now to the cycloaddition of bis(methylene)-2,3 bicyclo[2.2.1]heptane, *4*, to ethylene.

Scheme 4

Our application has been extended to this particular case, with a special emphasis placed on the differentiation of the possible reaction products. However, in view of the large size of the diene, the reaction pathway has not been calculated per se, but it has been deduced from that obtained for the model reaction. The motion of the atoms C_3, C_2, C_7, C_6, H_3, H_{31}, H_6, H_{61}, of the diene (Figure 2), and of the dienophile as well, was thus taken unchanged from the model reaction, and a rigid rotation analogous to that of H_b atoms of butadiene was used for the other atoms of the diene. By considering all the possible modes of the reaction: endo vs. exo attack (Color Plates 4a, 4b), Alder vs. anti-Alder orientation (Color Plates 4c, 4d), *ortho* vs. *meta* position in the adduct (Color Plates 4e, 4f), eight different products can be obtained from nonsymmetrically substituted

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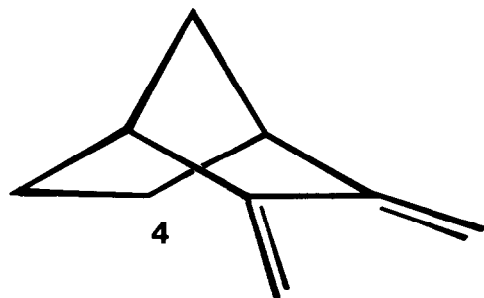
Scheme 4

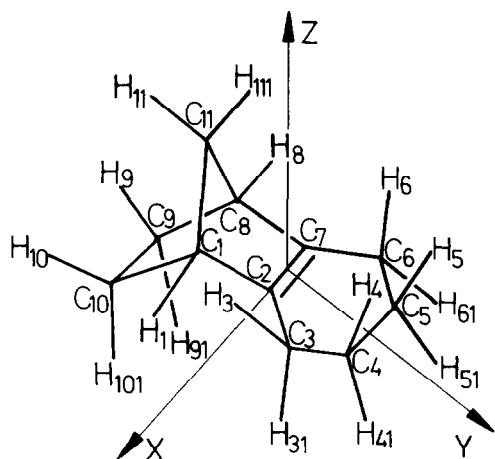*Figure 2. The adduct of the cycloaddition of 4 to 2*

dienes and dienophiles (Color Plate 5). Our application makes it possible to visualize the formation of all these products, which are easily differentiated by using colored substituents. Molecular graphics vividly summarizes the complex situation arising from the competition of several reaction pathways, which undoubtedly leads to a better understanding of the facial selectivity, stereo- and regioselectivity of this reaction.[7]

CONCLUSION

Clearly, such an application is in principle available only for users having physical access to a computer graphics facility of a similar configuration. However, once the information has been filmed or recorded on videotape, it then becomes a portable teaching device with a much greater impact than conventional pedagogical methods. To this end, we have made a 16mm film illustrating this application.[11] For technical reasons, the film was shot frame by frame, though the animation takes place in real time on the graphics system.

This application was developed mostly in order to popularize the use of molecular graphics in chemical education. Indeed, the potentials for and advantages of molecular graphics for visualizing step by step the detailed features of reaction mechanisms are so enormous that graphics is likely to become an indispensable tool for teaching chemistry.

ACKNOWLEDGEMENTS

REFERENCES

1 Dubois, J. E., Laurent, D. and Weber, J. *The Visual Computer*, 1985, **1**, 49–63

2 Hol, W. G. J. *Angewandte Chemie*, International Edition in English, 1986, **25**, 767–778

3 Barone, R. and Chanon, M. *Computer Aids to Chemistry*, Vernin, G. and Chanon, M., eds. Horwood, Chichester UK, 1986, 19–102

4 Weber, J. *Computer Aids to Chemistry*, Vernin, G. and Chanon, M., eds. Horwood, Chichester UK, 1986, 154–168

5 Weber, J., Roch, M., Combremont, J. J., Vogel, P. and Carrupt, P. A. *Journal of Molecular Structure THEOCHEM*, 1983, **93**, 189–200

6 Jefford, C. W., Mareda, J., Combremont, J. J. and Weber, J. *Chimia*, 1984, **38**, 354–356

7 Carrupt, P. A., Berchier, F. and Vogel, P. *Helvetica Chimica Acta*, 1985, **68**, 1716–1729

8 Houk, K. N., Lin, Y. T. and Brown, F. K. *Journal of the American Chemical Society*, 1986, **108**, 554–556

9 Brown, F. K. and Houk, K. N. *Journal of the American Chemical Society*, 1985, **107**, 1971–1978

10 Mottier, D. MS report, University of Geneva, 1986

11 Mottier, D. and Roch, M. *The Diels-Alder reaction: stereochemical study of a [4 + 2] cycloaddition*, 16mm film (10 min), University of Geneva, 1986. Video copies are available upon request to the authors.