

Mechanisms of Pericyclic Reactions: The Role of Quantitative Theory in the Study of Reaction Mechanisms

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The mechanisms of chemical reactions cannot be determined by experiment alone because reactions take place too quickly ($<10^{-13}$ s) for their course to be observed. The traditional "chemical" approach has been to use qualitative theory to predict possible mechanisms for a reaction and then to try to devise experiments to choose between them. Qualitative theory has, however, proved an unreliable guide in many cases and it is also not always possible to devise effective experimental tests.

Reaction mechanisms could in principle be predicted a priori, i.e. without any recourse to experiment, by solving the relevant Dirac or Schrödinger equations. Solutions of sufficient accuracy have, however, been obtained only for systems containing at most four electrons. The errors in the energies calculated for typical organic molecules, even using the best current ab initio treatments, amount to about one-fifth of the corresponding heats of atomization, >300 kcal/mol in the case of benzene.¹ Such a procedure clearly cannot be used to make a priori predictions of chemical behavior, and the gap is far too wide to be bridged by any foreseeable improvements in computers. Unless and until some better approach is developed,² there will be no question of chemical problems being solved a priori by quantum mechanical calculations.

Studies of reaction mechanisms have been one of the major concerns of our research group since its inception over 40 years ago, and the inadequacy of qualitative theories in this connection soon became clear. What was needed was a quantitative procedure that could reproduce the energies and geometries of molecules with adequate ("chemical") accuracy and could also be applied to quite large molecules at reasonable cost. Because no such procedures existed, we were forced to develop them ourselves. We followed the traditional "chemical" approach of trying to upgrade the accuracy of a very crude and correspondingly cheap procedure

by introducing parameters whose values are adjusted to fit experiment. While others had tried this so-called *semiempirical* approach and abandoned it as unpromising, we succeeded,³⁻⁵ and our latest semiempirical procedure (AM1⁶) is now being widely used.

According to current chemical theory, chemical behavior depends on differences in energy, etc., between closely related species, not on the absolute values for individual molecules. Thus chemical chemical equilibria are determined primarily by the differences in enthalpy between the reactants and products (heats of reaction), and the rate of a reaction is likewise determined primarily by its heat of activation, i.e. the difference in enthalpy between the reactants and the transition state (TS). These differences might be reproduced adequately by an intrinsically inaccurate procedure if the errors in the calculated energies cancelled. Such a procedure could be used to study reactions on an empirical basis, in areas where it had been tested.

This is, or should be, the basis for the so-called ab initio approach to chemistry, which has been followed almost universally by quantum theoreticians. Because ab initio treatments are supposedly based on mathematically rigorous approximations to the Schrödinger equation and contain no empirical parameters, their protagonists have claimed them to be inherently superior to semiempirical alternatives, even a very crude ab initio treatment being more to be trusted than any semiempirical one. This claim clearly has no basis so far as applications to chemistry are concerned. In this connection, ab initio methods are wholly empirical. The results from a given ab initio procedure can be trusted only in connections where tests have shown it to give satisfactory results. So far as chemistry is concerned, *all* current procedures are wholly empirical. The choice between them should be made solely on the basis of empirical tests and the amount of computing time they need.⁵

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Caoxian Jie was born in China on August 29, 1941 and received his B.S. degree at The Science and Technology University of Beijing in 1964, majoring in Chemical Physics. After 14 years at the Lanzhou Chemistry and Physics Research Institute, as Assistant Researcher and later Associate Researcher, he returned to Beijing, to Beijing Normal University, to work for a M.Sc. Degree, the highest degree available at universities in China at that time. On receiving the degree, in 1981, majoring in quantum chemistry, Jie was appointed to an Associate Professorship at Lanzhou University, a position which he still holds. However, he has spent most of the time since 1985 on leave of absence from Lanzhou University, working with Michael Dewar, first as a Research Associate at the University of Texas (1985-1988 and 1989-1990) and since 1990 as a Visiting Assistant in Chemistry at the University of Florida.

(1) The Hartree-Fock approximation leads to energies in error by $\sim 1\%$, due to the neglect of electron correlation. In the case of a typical organic molecule, the error is roughly the same as its heat of atomization. The best current procedures for estimating correlation energies reduce the error by less than 90%.

(2) As Boys concluded in 1958, and as was indeed already clearly known from earlier studies of H_2 , accurate results can be obtained only by using a wave function in which the interelectronic distances are explicitly included. Although Boys published a treatment of this kind which looked promising, no real progress has been made since his death.

(3) Dewar, M. J. S. *A Semiempirical Life*; American Chemical Society: Washington, DC, 1992.

(4) Dewar, M. J. S. (a) *J. Mol. Struct.* 1983, 100, 41. (b) Dewar, M. J. S. *J. Phys. Chem.* 1985, 89, 2145. (c) Dewar, M. J. S. *Int. J. Quantum Chem.* 1988, 22, 557.

(5) Dewar, M. J. S. *Int. J. Quantum Chem.* 1992, 44, 427.

(6) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* 1985, 107, 3902.

Nearly all current *ab initio* procedures start with a Hartree-Fock-type (HF) calculation, using the Roothaan-Hall (RH) approximation in which MO's are approximated by linear combinations of an assumed set of approximate AO's (*basis set*). HF-type RH procedures fail to reproduce heats of atomization, indicating that large changes in correlation energy occur during the formation of chemical bonds.^{7,8} However, they usually give quite reasonable predictions of heats of reaction for reactions involving neutral closed-shell molecules, even if small basis sets are used. The net change in correlation energy due to bonding in a given closed-shell system evidently tends to depend on the number of bonds being formed, not on the way the bonds are distributed among the atoms in question. As might be expected in view of this, HF-type *ab initio* procedures also often give good estimates of the geometries and other ground-state properties of such species, and they also lead to reasonable estimates of the activation barriers for processes in which the number of bonds remains unchanged throughout, e.g. the barrier to CN rotation in amides or the barrier to inversion in ammonia.

However, large errors naturally occur in HF-type studies of reactions where bonds are being formed and/or broken and in calculations for ions, which can be regarded as products of heterolytic bond cleavage. Since the errors are due to changes in correlation energy, correlated procedures must be used in such cases, and since the fraction of the correlation energy that can be recovered depends on the size of the basis set, large basis sets usually have to be used. Calculations at this level are currently feasible only for reactions of very small molecules. Indeed, these conclusions rest primarily on calculations, notably by Schaefer's group, for reactions simple enough for very high level *ab initio* methods to be used.

The majority of the *ab initio* calculations that have been reported for chemical reactions have nevertheless been carried out using simple HF-type procedures and small basis sets because no better alternative was feasible. Indeed, other unjustifiable simplifications are also commonly made in order to save computing time.⁹ Calculations have also usually been restricted to the simplest example of the reaction in question, which is often untypical and for which experimental data are often lacking. Yet the results are commonly presented as reliable conclusions from quantum theory, more to be trusted than those given by any semiempirical procedure.

Claims of this kind have naturally caused us problems. The fact that the treatments used are in fact wholly empirical, so far as chemistry is concerned, is clearly not implied by the loaded term "*ab initio*", and the claim that such procedures are "*nonempirical*" has been used as an excuse for not testing them. Indeed, the only systematic tests so far reported for the *ab initio* models that are being currently misused in this way

(7) Synder, L. C.; Basch, H. *Molecular Wave Functions and Properties*; Wiley: New York, 1972.

(8) Dewar, M. J. S.; Storch, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 3898.

(9) A common but particularly deplorable example is to recalculate the energy of a molecule by a high level procedure, using the geometry given by a simpler and hence cheaper one ("single point" calculation). A procedure which gives poor estimates of energies cannot be relied on to give good estimates of geometries. Single point calculations are acceptable only if justified by specific evidence.

have been ones carried out by our group^{8,10} in order to compare our procedures with *ab initio* ones. Equally, the description of our procedures as "*semiempirical*" has seemingly degraded their value because most of the other standard semiempirical treatments are either grossly inaccurate and unreliable (e.g. CNDO/2) or are restricted to calculations of specific properties (e.g. SPINDO). It has been difficult for us to convince other chemists that such a situation exists because of the tendency to believe the "*experts*" in areas other than one's own and because the *ab initio* conclusions usually agree with current chemical theory. What we needed was a case where our procedures led to conclusions that differed in major respects from those currently accepted by chemists and supported by *ab initio* calculations, where we could show by extensive comparisons with experiment that we were right, and where the revisions brought about by our work were both striking and significant.

Pericyclic reactions¹¹⁻¹⁴ seemed to offer good possibilities in this connection because most of them can take place in more than one way, because the choice between the alternatives is usually by no means obvious, and because numerous experimental results are available for comparison. Furthermore, earlier DG studies of the Cope rearrangement¹⁵ and the Diels-Alder reaction^{16,17} had suggested that the currently accepted views concerning their mechanisms were probably wrong. We therefore decided to reexamine some of these reactions in detail, taking advantage of the advances in computational technology that had been made by our group.

The Cope Rearrangement

The Cope rearrangement of 1,5-hexadiene (1) was discovered¹⁸ in 1941, soon after Evans¹⁴ had given his seminal interpretation of the Diels-Alder reaction in terms of a synchronous¹⁹ mechanism involving an aromatic transition state (TS). Cope represented his new reaction likewise in terms of a concerted cyclic interchange of bonds round a C₆ ring, corresponding, in current terminology, to a synchronous "*allowed*" pericyclic mechanism with an aromatic TS (2). Analogy with the Diels-Alder reaction seemed to leave no doubt concerning the correctness of this interpretation because the Cope rearrangement of 1 is one of the very few

(10) Dewar, M. J. S.; O'Connor, B. M. *Chem. Phys. Lett.* **1987**, *138*, 141.

(11) The term "*pericyclic*" was introduced by Woodward and Hoffmann¹² to describe reactions that involve a cyclic interchange of bonds round a ring of atoms. However, the possibility that reactions might take place in this way, by a cyclic interchange of bonds round a ring of atoms, had been considered many years earlier. See refs 13 and 14.

(12) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(13) (a) Evans, M. G.; Warhurst, E. *Trans. Faraday Soc.* **1938**, *34*, 614.

(b) Evans, M. G. *Trans. Faraday Soc.* **1939**, *35*, 824.

(14) Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761.

(15) Dewar, M. J. S.; Ford, G. P.; McKee, M. L.; Rzepa, H. S.; Wade, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 5069.

(16) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650.

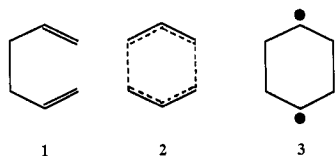
(17) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771.

(18) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441.

(19) A *concerted* or *one-step* reaction is one which takes place in a single kinetic step. A *synchronous* reaction is a concerted reaction in which all the changes in bonding take place in parallel. A *two-stage* reaction is concerted but not synchronous, some of the changes in bonding taking place during formation of the transition state (TS) and the others during conversion of the TS to the product(s).

pericyclic reactions in which the choice between synchronous and nonsynchronous mechanisms is not biased by steric or stereoelectronic effects.

In 1971 Dewar and Wade²⁰ reported an experimental study of several Cope rearrangements which strongly supported an alternative two-stage¹⁹ mechanism which Doering et al.²¹ had suggested as a possibility, involving a biradical-like TS (3) in which the C₁C₆ bond has formed while the C₃C₄ bond still remains intact. Further support was provided by MINDO/3 calculations¹⁵ for the rearrangement of 1, the predicted lengths (161 pm) of the C₁C₆ and C₃C₄ bonds in the TS being much less, and those (144 pm) of the other CC bonds greater, than the values that would be expected for 2. While the calculated geometry showed that the TS was not a classical 1,4-hexylene biradical, as the classical structure 3 indicates, it corresponded to that expected for a biradicaloid²² derived from 3 by a strong σ conjugative²³ through-bond interaction between the radical centers. Indeed, the fact that good estimates of activation energies were obtained for both the boat and the chair Cope rearrangements of 1, using the normal RHF version of MINDO/3, showed that the C₂C₅ interaction must be strong enough to make the TS behave like a closed shell species.



In 1984, Osamura et al.²⁴ challenged this conclusion on the grounds that MCSCF ab initio calculations, using the 4-31G basis set, indicated the TS to be 2, not 3. While their work was open to technical criticisms,²⁵ a subsequent rigorous treatment of the same kind²⁶ led to similar conclusions, together with an estimate (>20 kcal/mol) of the difference in energy between the aromatic (ARO) and biradical-like (BR) TSs.

We therefore reexamined²⁵ the problem, using the AM1 procedure³ which had been developed in the meantime. Calculations were carried out for the boat and chair rearrangements of 1 and for the chair rearrangements of its 2-phenyl (4a), 2,5-diphenyl (5a), 2-methyl (4b), 3-phenyl (6a), 3-methyl (6b), and 2,4-diphenyl (7) derivatives. All these reactions were predicted to take place by the biradicaloid (BR) mechanism, a conclusion strongly supported by comparison of the calculated and observed enthalpies of activation and by comparison with experiment of secondary deuterium kinetic isotope effects (SDKIE) calculated for 1, 4a, and 5a.

However, one curious anomaly remained. If the mechanisms of the boat and chair rearrangements of 1 are similar, so too should be the corresponding

(20) Dewar, M. J. S.; Wade, L. E., Jr. *J. Am. Chem. Soc.* 1977, 99, 4417.

(21) Doering, W. v. E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* 1962, 18, 67.

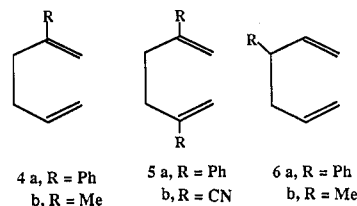
(22) A biradicaloid is a singlet biradical in which through-bond coupling between the radical centers is so strong that the system behaves in many respects as a closed shell species.

(23) Dewar, M. J. S. *J. Am. Chem. Soc.* 1984, 106, 669.

(24) Osamura, Y.; Kato, S.; Morokuma, K.; Feller, D.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* 1984, 106, 3362.

(25) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* 1987, 109, 5893.

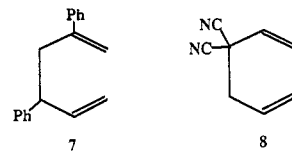
(26) Morokuma, K.; Borden, W. T.; Hrovat, D. A. *J. Am. Chem. Soc.* 1988, 110, 4474.



4 a, R = Ph
b, R = Me

5 a, R = Ph
b, R = CN

6 a, R = Ph
b, R = Me



7

8

entropies of activation, and all the reported calculations had indeed predicted this to be the case. The experimental values were in fact quite different (chair, -13.1 ± 1.0 ; boat, -3.0 ± 3.5 eu²⁷). The MINDO/3 (-17.0 eu) and AM1 (-15.6 eu) values agreed with those for the chair, but not the boat, while the ab initio values reported by Morokuma et al.²⁶ (chair, -9.0 ; boat, -6.2 eu) erred in the opposite direction. The discrepancies could not be attributed to experimental error because Doering and Troise²⁸ found comparably small entropies of activation (3–6 eu) for other boat Cope rearrangements. Equally, since extensive tests have shown that our procedures usually reproduce entropies of molecules, and entropies of activation, to within 2 eu, and since the agreement for the chair Cope rearrangement of 1 was satisfactory, the discrepancy seemed unlikely to be due to error on the part of AM1.

This problem was apparently solved by our discovery²⁹ of what appeared to be a second boat TS, with an ARO-type geometry and an entropy in agreement with experiment. While its energy was greater by 2.7 kcal/mol than that of the BR TS, the calculated difference in entropy was sufficient to outweigh this at the temperatures used in the kinetic measurements. These results seemed to indicate clearly that the entropies of activation for the boat and chair rearrangements of 1 are different because their mechanisms are different, the chair rearrangement being of BR type and the boat rearrangement of ARO type.

The possibility that a one-step reaction might take place in two different ways, via two distinct TSs, had of course been recognized as a theoretical possibility. However, no example had been reported, other than the irrelevant case of narcissistic reactions where there are pairs of equivalent mirror-image TSs. We were moreover able to find a second apparent TS in the rearrangements of 3,3-dicyano-1,5-hexadiene (8),³⁰ semi-bullvalene (9),³¹ and bullvalene (10).³¹ In 8, as in 1, the BR TS was the lower in energy, but only by 0.9 kcal/mol, a difference far too small to outweigh its more negative entropy. Comparison of the observed SDKIEs with those calculated for the BR and ARO rearrangements indicated that this reaction is indeed of ARO type. In 9 and 10, the ARO TS was the lower in energy, due no doubt to a decrease in ring strain during its formation. Further support for our conclusions was

(27) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* 1972, 94, 7147.

(28) Doering, W. v. E.; Troise, C. A. *J. Am. Chem. Soc.* 1985, 107, 5739.

(29) Dewar, M. J. S.; Jie, C. *J. Chem. Soc., Chem. Commun.* 1987, 1451.

(30) Dewar, M. J. S.; Jie, C. *J. Chem. Soc., Chem. Commun.* 1989, 98.

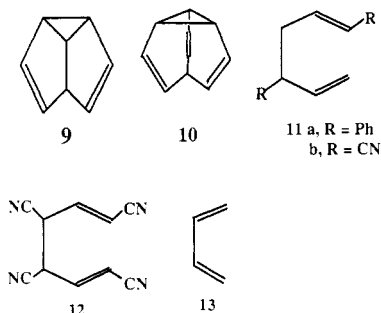
(31) Dewar, M. J. S.; Jie, C. *Tetrahedron* 1988, 44, 1351.

Table I. AM1 Calculations for Cope Rearrangements

molecule	type of TS	ΔH^a	ΔH^b	ΔS^c	$R(CC)^d$
5b	BR	82.0	29.8	-11.9	1.586; 1.747
8	BR	94.2	34.6	-23.0	1.685; 1.712
8	ARO	(94.2)	35.5	-7.6	2.044
11a	BR	70.6	41.0	-10.0	1.687
11a	ARO	(70.6)	42.5	-14.8	2.007
11b	BR	81.5	40.6	-12.8	1.685
11b	ARO ^e	(81.5)	42.3	-8.4	1.983
12	ARO	150.5	41.2	-8.7	2.133
13	ARO	146.3	20.8	+1.2	2.232
1 (chair)	BR	18.6	37.1	-15.6	1.656
1 (chair)	ARO ^f	(18.6)	43.6	-8.1	1.992
1 (boat)	BR	(18.6)	47.8	-11.0	1.661
1 (boat)	ARO ^f	(18.6)	50.5	-6.3	1.983

^a Heat of formation (kcal/mol). ^b Heat of activation (kcal/mol). ^c Entropy of activation (eu; cal K⁻¹ mol⁻¹). ^d Lengths (Å) of the C₁C₆ and C₃C₄ bonds. ^e Marginal TS; gradient indistinguishable from zero. ^f Point of inflexion.

provided by SCFCI-type ab initio calculations for 1 by Dewar and Healy³² which showed that the relative stability of the BR TS is grossly underestimated if a sp-type basis set (3-21G or 6-31G) is used.



At this point the mechanisms of these reactions seemed to have at last been established beyond reasonable doubt. However, Borden et al.³³ have recently reported ab initio HF calculations, using the 3-21G basis set, which, they claim, show the chair rearrangement of 1 to be of ARO type. Although they gave references to our papers, and to the paper by Dewar and Healy noted above,³² they ignored their contents, apart from a footnote stating that they had been unable to confirm our claim of a second (ARO) TS on the AM1 potential energy (PE) surface for the chair rearrangement of 1. Although the existence of this TS had no bearing on our mechanistic arguments, we nevertheless reexamined the reactions we had previously studied, and since the results were interesting and unexpected, we also carried out calculations for the chair Cope rearrangements of 2,5-dicyano-1,5-hexadiene (5b), 1,4-diphenyl-1,5-hexadiene (11a), 1,4-dicyano-1,5-hexadiene (11b), and 1,3,4,6-tetracyano-1,5-hexadiene (12). The results are summarized in Table I, which also includes our earlier results for the boat and chair rearrangements of 1.

The potential energy surfaces (PES) for these reactions are bisected by ridges which form the reaction barriers. A minimum (col) in the ridge corresponds to a TS. Figure 1a shows a section of the PES along the barrier ridge for the chair Cope rearrangement of 1, taking the length of the C₁C₆ or C₃C₄ bond as the horizontal coordinate. This plot corresponds to a profile

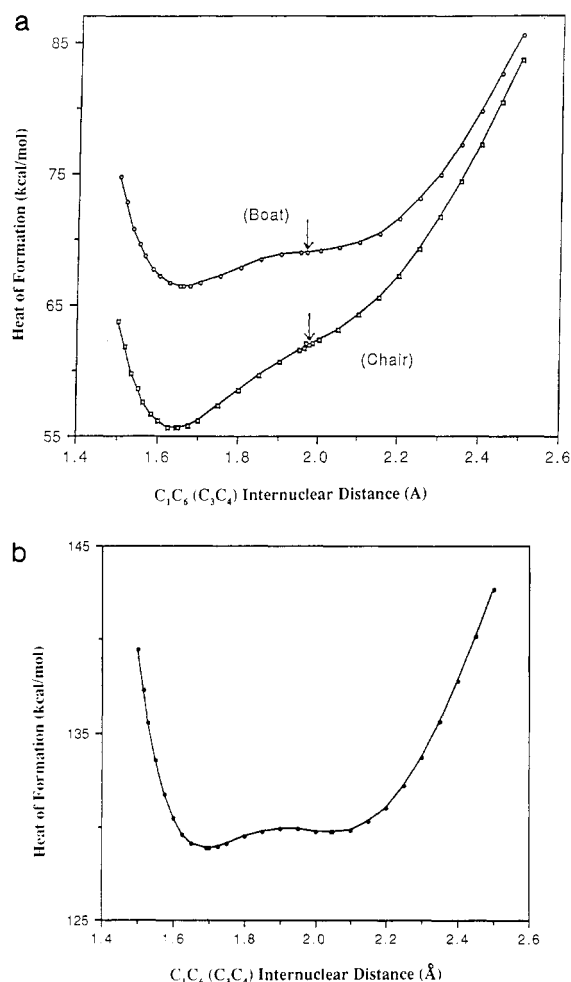


Figure 1. Reaction barrier profiles (a) for the boat and chair Cope rearrangements of 1 and (b) for the chair Cope rearrangement of 8. Points of inflexion (POI) are indicated by arrows.

of the barrier ridge as seen from the reactant or product. The profile has only one minimum, so there is indeed only one TS, as Borden et al. claimed. However, the shape of the profile clearly corresponds to a superposition of two minima, corresponding to two distinct reaction paths, the higher energy TS being consequently replaced by a point of inflexion (POI). This interpretation was supported by the barrier profiles for the boat rearrangement of 1 (Figure 1a) and the chair rearrangement of 8 (Figure 1b). The latter exhibits two distinct minima, corresponding to two distinct TSs, while the former is a borderline case, the gradient at the POI being zero within the limits of accuracy of the calculation. Our conclusions concerning the duality of mechanism in these reactions were therefore correct, but not our claims concerning the existence of two distinct TSs in each of them. Of the reactions studied, those of 8 and 11a showed two genuine TSs, while that of 11b was another borderline case, the gradient at the POI being indistinguishable from zero.

Our misidentification of POIs as TSs was due to use of the McIver-Komornicki³⁴ (MK) procedure, where TSs are located by minimizing the scalar gradient of the energy. While it was known in principle that the MK procedure converges at such POIs as well as at TSs, no example had been previously reported. It did

(32) Dewar, M. J. S.; Healy, E. F. *Chem. Phys. Lett.* 1987, 141, 521.

(33) Borden, D. A.; Borden, W. T.; Vance, R. L.; Randon, K. N.; Houk, K. N.; Morokuma, K. *J. Am. Chem. Soc.* 1990, 112, 2018.

(34) McIver, J. W.; Komornicki, A. *Chem. Phys. Lett.* 1971, 10, 303; *J. Am. Chem. Soc.* 1972, 94, 2625.

not therefore occur to us that there was any need to look further, given that the scalar gradients at the POIs were small in nearly all cases and indistinguishable from zero in the key reaction, the boat rearrangement of 1.

This work seems to have removed the last possible doubts concerning the mechanisms of the boat and chair Cope rearrangements of 1. These reactions can therefore now serve as a useful test of theoretical procedures. Seen in this light, a recent study of 1 by Dupuis, Murray, and Davidson³⁵ provides further evidence concerning the limitations of current *ab initio* methods.

Dupuis et al. began with an MCSCF calculation analogous to that of Morokuma et al.²⁶ but using a spd-type basis set (6-31G*). The results were then used as the basis for extensive CI calculations. Dupuis et al. agreed with us in finding two paths, one BR and the other ARO, for the chair rearrangement and they also agreed in finding the BR TS to be the lower in energy. However, they failed to find a BR TS for the boat rearrangement and the difference between the activation energies calculated for the BR and ARO chair paths was too small to outweigh the expected difference in entropy between them. Even the estimates of relative energies were far from accurate, the calculated activation energies for the boat and chair rearrangements each being too large by ~10 kcal/mol. Furthermore, since the heat of dissociation of 1 into a pair of allyl radicals was underestimated by a similar amount and since the entropy of dissociation is far more positive than either entropy of reaction, their results, taken at face value, predict dissociation of 1 into allyl radicals to be much faster than either mode of rearrangement.

Thus although these calculations were carried out at a relatively high level, they still failed to reproduce essential features of the reaction and the numerical agreement with experiment was poor. This study of the reactions of 1 must, moreover, have required far more computing time than all our extensive surveys of Cope rearrangements put together. However, it has served a useful purpose by demonstrating beyond doubt the inadequacy of the earlier *ab initio* studies in this connection and hence, by inference, the use of such procedures in studies of other reactions.

The fact that AM1 remains the only treatment that has passed our test does not of course mean that it will necessarily be right in all cases. It does, however, mean that *ab initio* studies of reactions are pointless in cases where AM1 can be used effectively, except as a supplement to AM1 to clarify specific points which AM1 calculations have left uncertain. Such *ab initio* calculations usually need to be carried out at a high level to be significant.

Biradical-like Intermediates and Transition States

Our conclusions concerning the Cope rearrangement were startling because it had become generally accepted that "allowed" pericyclic reactions invariably take place by synchronous ARO mechanisms unless specifically prevented from doing so. This indeed was stated specifically by Woodward and Hoffmann in their classic review.¹² Other "allowed" pericyclic reactions usually present a similar choice between synchronous (ARO)

and nonsynchronous (BR) mechanisms, and AM1 calculations by our group have predicted the BR mechanism to be preferred in most cases.³ These conclusions were, however, weakened by a technical problem. As we have already noted, BR TSs are biradical-like species and such species cannot usually be treated satisfactorily by the usual RHF version of AM1. The Cope rearrangement is an exception because the through-bond coupling between the "unpaired" electrons in the BR TS is exceptionally strong. In most other cases, open-shell versions of AM1 have to be used, and these are liable to overestimate the stabilities of biradicals.^{16,36} The fact that such studies have often predicted BR mechanisms is therefore of uncertain significance in itself. However, there are good reasons for believing that one of the most important reactions of this kind, namely the Diels–Alder reaction, is usually of BR type.

The Diels–Alder Reaction

The Diels–Alder (DA) reactions between butadiene (13) and ethylene or its monocyano or dicyano derivatives were predicted¹⁶ to be of BR type by an open-shell (CI) version of AM1. Reasonable estimates of their relative activation energies were obtained in this way, whereas AM1 itself failed, and analogous studies of several other DA reactions have been reported by Dannenberg.^{37,38} The BR mechanism is also supported by two other lines of evidence.

(a) According to current qualitative theory, in particular PMO theory^{39,40} proper,⁴¹ any substituent in the 1-, 3-, or 6-position of the BR TS (14) should stabilize it relative to the ARO TS (15) while substituents in the 4- or 5-position should have the opposite effect. The modes of addition of unsymmetrically substituted dienes to unsymmetrically substituted dienophiles can be predicted with complete assurance in this way,⁴⁰ problems arising only if steric repulsions intervene or if the mode of addition depends on quantitative differences between the effects of competing substituents. Interpretations in terms of a synchronous ARO mechanism fail if the diene and dienophile both contain +E (electron-attracting conjugative) substituents, e.g. COOH.

(b) Bernardi et al.⁴² have recently studied the DA reaction between 13 and ethylene, using a procedure similar to that used by Morokuma et al.²⁶ Two TSs were located, one the usual symmetrical ARO structure and the other a biradical-like BR-type species in which one of the new CC bonds was almost completely formed while the other was still very long (300 pm). The BR TS was the higher in energy, but only by 2 kcal/mol. Since application²⁶ of the same approximation to the

(36) Dannenberg, J. J. *Adv. Mol. Modelling* 1990, 2, 1.

(37) Branchadell, V.; Ortí, J.; Ortuño, R. M.; Oliva, A.; Font, J.; Bertrán, J.; Dannenberg, J. J. *J. Org. Chem.* 1991, 56, 2190.

(38) Kalla, N.; Franck, R. W.; Dannenberg, J. J. *J. Org. Chem.* 1989, 54, 4206.

(39) Dewar, M. J. S. *J. Am. Chem. Soc.* 1952, 74, 3341, 3345, 3350, 3353, 3355, 3357.

(40) Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*, Plenum Publishing Corp.: New York, 1975.

(41) The term "PMO" was invented by Dewar to describe a general qualitative treatment of chemistry, based on the results in ref 39. It was later misappropriated to describe a different and more limited use of the basic theory.

(42) Bernardi, F.; Bottoni, A.; Robb, M. A.; Field, M. J.; Hillier, I. H. Guest, M. F. *J. Chem. Soc., Chem. Commun.* 1985, 1051.

(35) Dupuis, M.; Murray, C.; Davidson, E. R. *J. Am. Chem. Soc.* 1991, 113, 9756.

Cope rearrangement of 1 led to an estimate of the relative energy of the BR TS that was too large by at least 20 kcal/mol, there is clearly a very strong presumption that the parent Diels–Alder reaction takes place by the BR mechanism.

Borden et al.⁴³ have nevertheless recently claimed that *ab initio* HF/3-21G calculations of secondary deuterium kinetic isotope effects (SDKIE) for a number of simple Diels–Alder reactions support the ARO mechanism. They ignored the evidence to the contrary, summarized above, including the demonstrated inadequacy of the 3-21G basis set in the case of a closely related reaction. Borden et al. reported no comparisons of activation parameters and the agreement between the calculated and observed SDKIEs was not impressive.

Borden et al. argued that the agreement was nevertheless better than it would have been for the BR mechanism because UHF/3-21G calculations, starting with the RHF ARO geometries, gave quite different results. The fallacy in this argument is obvious. If the BR and ARO TSs correspond to different minima on the PES, the procedure used by Borden et al. would necessarily lead to the UHF ARO TS, even if the UHF BR TS were the lower in energy.

Theory of Pericyclic Reactions: The Multibond Rule

The existence of dual independent reaction paths in Cope rearrangements is surprising. Why do the paths not coalesce into a single intermediate path of normal type? This would be understandable if the BR route corresponded to a reaction which was “forbidden” by the Woodward–Hoffmann rules¹² or involved an antiaromatic TS,¹⁴ but this is not the case, and the fact that the BR route is usually preferred seems even more surprising.

The solution of the first problem was given some time ago in the paper²¹ reporting MINDO/3 calculations for the Cope rearrangement of 1. This reaction could take place via a singlet biradical (3), with C_{2v} symmetry, in which two electrons occupy two degenerate MO's, Φ^+ and Φ^- . Biradicals of this kind are, however, unstable⁴⁴ because they have degenerate ground states.⁴⁵ An appropriate geometric distortion, retaining C_{2v} symmetry, will remove the degeneracy, leading to a more stable closed-shell species in which the two electrons occupy the lower in energy of the two originally degenerate MO's. Since different distortions can make either Φ^+ or Φ^- the lower in energy, two distinct *Jahn–Teller*^{44,45} isomers can be generated in this way, one corresponding to occupation of Φ^+ and the other to occupation of Φ^- and each corresponding to a TS or stable intermediate in the reaction. Interconversion of the two isomers involves a HOMO/LUMO crossing, i.e. that of Φ^+ and Φ^- , and is therefore “forbidden”. A simple PMO analysis²¹ indicates that in the case of 3, one of the isomers corresponds to the TS or symmetrical intermediate in the BR reaction whereas the other

isomer corresponds to the ARO TS. Since the ARO reaction is a typical “allowed” synchronous process, no orbital crossing takes place during it. Formation of the BR intermediate or TS from 1 therefore involves a HOMO/LUMO crossing and is consequently “forbidden”. Both isomers therefore exist as distinct species.

The BR rearrangement of 1 is therefore a two-step or two-stage¹⁹ process in which each of the steps or stages involves a HOMO/LUMO crossing and is consequently “forbidden”. Thus the Cope rearrangement of 1 takes place by a route involving two successive “forbidden” reactions rather than by a single synchronous one, in flagrant violation of the Woodward–Hoffmann rules¹² and Evans' principle.¹⁴

The existence of HOMO/LUMO crossings during the BR rearrangements of 1 and several derivatives of 1 has been confirmed by analysis of the eigenvectors given by our AM1 calculations. It seems very likely that a similar situation will be found to hold in other BR-type pericyclic reactions. All these reactions therefore take place in the same doubly “forbidden” manner.

The explanation for this seemingly strange result was given some years ago⁴⁶ in terms of a new rule relating to the mechanisms of multibond reactions, a multibond reaction being one in which two or more covalent bonds are formed and two or more broken. A simple Evans–Polanyi-type analysis indicated that the activation energy of a synchronous two-bond reaction should be roughly double that of an analogous one-bond reaction, and synchronicity should become progressively more unfavorable, the greater the number of bonds involved. Multibond reactions therefore tend not to be synchronous, preferring to take place in steps or stages,¹⁹ each of one-bond type (*multibond rule*⁴⁶). Exceptions occur only if no appropriate intermediates with low enough energies are available or if some factor specifically assists synchronicity.

Pericyclic reactions are by their nature multibond processes and would therefore be expected to be nonsynchronous. In the case of an “allowed” pericyclic reaction, however, the synchronous mechanism will be assisted by the aromatic stabilization of the corresponding ARO TS. Whether or not this will be sufficient to overcome the inherent disadvantage or synchronicity will depend on the relative energy of the intermediate biradical-like intermediate involved in the alternative two-step or two-stage BR mechanism. The course of such reactions cannot therefore be predicted by qualitative theories and it is unlikely to be subject to any kind of universal generalization of the kind embodied in the Woodward–Hoffmann rules.

Implications for Chemistry

The work reviewed and reported here has led to a complete revision of ideas concerning the mechanisms of pericyclic reactions. It also has major implications concerning theoretical chemistry in general.

A. Need To Eliminate Alternative Mechanisms. It has been generally assumed in the past that a one-step reaction has a unique TS and that finding a TS for a reaction is sufficient to establish its mechanism. Now that an exception has been found, this assumption

(43) Borden, D. A.; Borden, W. T.; Vance, R. L.; Randon, N. G.; Houk, K. N.; Morokuma, K. *J. Am. Chem. Soc.* 1990, 112, 2018.

(44) Dewar, M. J. S.; Kirschner, S.; Kollmar, H. W.; Wade, L. E. *J. Am. Chem. Soc.* 1974, 96, 5242.

(45) The Jahn–Teller theorem applies to models based on approximate quantum mechanical treatments. The conclusions apply of course only to the model in question.

(46) Dewar, M. J. S. *J. Am. Chem. Soc.* 1984, 106, 209.

can no longer be made without specific justification. In future it will also be necessary to show that no alternative reaction paths exists, corresponding to a greater rate of reaction. This very greatly increases the amount of computation needed.

B. Relation between TSs and POIs. In cases where the higher energy TS is replaced by a POI with a low gradient, the energy and geometry corresponding to the POI are similar to those for the corresponding (hidden) higher energy TS; cf. Figures 1a, 1b, and 2b. Thus if the MK procedure converges on a POI, and if the gradient there is small, the geometry and energy found for the POI should be good approximations to those of the corresponding "masked" TS. Indeed, the boat and chair ARO POIs from 1, and the ARO TSs from 8 and 11a, all have similar geometries; see Table I. Under these conditions, the vibration frequencies calculated for a POI should also be similar to those of the masked TS, except for motion along the ridge where the corresponding "force constant" vanishes. Because the AMPAC program neglects vibrations with zero force constants in calculating partition functions, the entropy calculated for the POI should also correspond quite well to that expected for the corresponding masked TS. These arguments are supported by the success of our calculations for 1, according to which the (masked) ARO TS provides an easier path for the boat rearrangement than does the (real) BR TS, due to the difference in entropy between them.

C. Need for a Quantitative Theory. The work reported here has invalidated the current treatment of

pericyclic reactions in terms of the Woodward-Hoffmann rules¹² or Evans' principle.^{13,14} The course of such reactions is now seen to depend on the interplay of opposing factors whose contributions cannot be determined by experiment or estimated by using qualitative theories. There is clearly a need for a quantitative theoretical treatment and work by our group has shown a similar need to exist in many other areas of chemistry.³ We are indeed at the beginning of a new era where quantitative quantum chemical calculations will necessarily form part of a chemist's standard armoury.

To be useful in this connection, the procedure used must be sufficiently accurate and reliable and calculations must be possible for the molecules in which chemists are directly interested, using readily available computers. The calculations must also be carried out by chemists themselves, rather than as a service by theoreticians. Magnetic resonance spectroscopy would have proved far less useful in chemistry if it had remained in the hands of the physicists who originally developed it.

The only procedures that meet these conditions at present are the semiempirical ones developed by our group, AM1 being currently the method of choice.⁵ Improvements in computers would now permit the development of better procedures of this kind. Indeed, we ourselves have just completed the development of the first of a new family of such treatments.⁴⁷

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(47) Dewar, M. J. S.; Jie, C. To be published.