CENTENARY LECTURE*

Organic Reactions Paths: A Theoretical Approach

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1 Introduction

The greatest single contribution to the clarification of the chemist's conception of valence, the Heitler and London paper on H_2, appeared in *Zeitschrift für Physik* on June 30, 1927.

This statement, quoted from Pauling and Wilson's 'Introduction to Quantum Mechanics; goes back to 1935, but it still preserves its full validity. Indeed, the quantum mechanical treatment of molecules and their interactions is the only way to convert chemistry from a collection of empirical notions to a deep understanding based on the fundamental laws of nature. In that famous work the energy of two hydrogen atoms forming a hydrogen molecule was calculated as a function of their distance: the process can be taken as an example of chemical reaction: indeed almost all chemical reactions involve the formation and/or the breaking of one or more bonds.[1] Of course much more complex electronic and nuclear changes can be involved than those occurring in hydrogen formation. Since the early days, quantum chemistry has developed an ever increasing number of theoretical methods to deal with the problem of reactivity, together with efficient computational techniques, implemented over more and more powerful electronic computers. Two different levels can be neatly recognized: the calculation of potential surfaces for chemical systems, from which the activation barrier for different reaction paths from reactants to products can be envisaged and the calculation of trajectories over such potentials, each trajectory corresponding to given initial conditions. From an appropriate number of such calculations, reaction rate constants can be evaluated.

This lecture will be almost exclusively restricted to the first level. In this particular field a few theoretical methods are used extensively. I shall mention, and use, the molecular orbital approach, at different levels of sophistication, the empirical or *ab initio* valence-bond method, and molecular mechanics. It must be kept in mind that most theoretical calculations deal with isolated molecules or with pairs of approaching molecules: this is an appropriate model for the study of gas-phase reactions, while most chemical experiments are carried on in condensed

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[1] M. Simonetta, 'Bond formation and breaking: the heart of chemistry', in 'Horizons of Quantum Chemistry', ed. K. Fukui and B. Pullman, R. Reidel Publ. Co., Dordrecht, 1979, p.51.

phases. The present review will consider, in succession, calculations for isolated molecules, for molecules present in a solvent, and reactions in the solid state. The field of reactions on surfaces, though of extreme interest due to the connection with heterogeneous catalysis, has had to be sacrificed for the sake of brevity. Most examples are taken from organic chemistry, since they have been chosen on the basis of personal experience, but the same or similar theoretical approaches can be used to investigate inorganic or metallic reactions.

2 Isolated molecules

A particularly simple reaction is the dissociation of LiH to Li and H atoms in their ground states:[2]

$$\mathrm{LiH}(^1\Sigma^+) \longrightarrow \mathrm{Li}(^2S) + \mathrm{H}(^2S) \qquad (1)$$

This is a four-electron problem and the potential energy depends only on one geometrical co-ordinate, the Li—H distance, so that calculations of high accuracy are feasable here. We used an *ab initio* valence bond (V.B.) technique[3] based on orbitals that are linear combinations of all the functions in the basis set, the perfect-pairing orbitals. The energy is obtained at fixed interatomic distances within the Born–Oppenheimer approximation. The perfect-pairing orbitals also depend on the distance. An example is shown in Figure 1. An excellent description

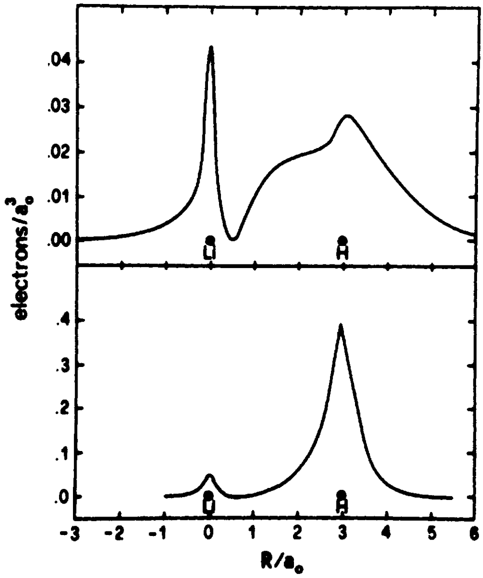

Figure 1 *Valence perfect-pairing orbitals for* LiH; LiH *intermolecular distance* 3.015 a.u.

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[2] C. Gatti, S. Polezzo, M. Raimondi, and M. Simonetta, *Mol. Phys.*, 1980, **41**, 1259.

[3] M. Simonetta, E. Gianinetti, and I. Vandoni, *J. Chem. Phys.*, 1968, **48**, 1579.

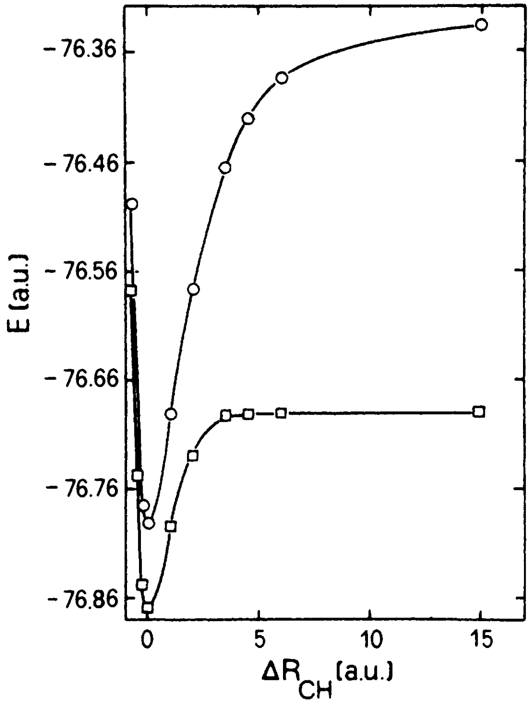

Figure 2 *Potential energy as a function of the* C—H *distance in different approximations:* ○ *SCF;* □ *V.B.*

of the ground and excited states is obtained, together with the correct behaviour along the dissociation path. The calculated dissociation energy for the $X^1\Sigma^+$ state is 2.524 eV to be compared with the experimental value 2.515. The anomalous Birge–Sponer curve for the $A^1\Sigma^+$ state is correctly reproduced.

An *ab initio* V.B. technique was also applied to the reaction:

$$C_2H_2(^1\Sigma^+) \longrightarrow C_2H(^2\Sigma^+) + H(^2S) \qquad (2)$$

and led to excellent values for the dissociation energy, the C—H equilibrium distance, and vibrational properties. Figure 2 shows the improvement with respect to a self-consistent field calculation.

V.B. theory has been useful in the study of the collinear approach of two $CH(^2\Pi)$ radicals to form $^1\Sigma^+$ acetylene:[4]

$$CH(^2\Pi) + CH(^2\Pi) \longrightarrow C_2H_2(^1\Sigma^+) \qquad (3)$$

The electron pairing has to change during the reaction, since each reactant has only one unpaired electron but three unpaired electrons from each fragment are needed

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[4] M. Raimondi, M. Simonetta, and J. Gerratt, *Chem. Phys. Lett.*, 1981, **77**, 12.

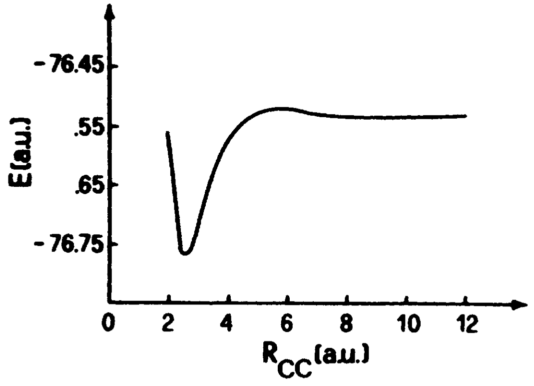

Figure 3 *Energy of acetylene molecule as a function of the* C—C *distance*

to form the triple bond in the product; considerable recoupling is necessary. One technical problem is the construction of spin functions for the molecule from spin functions for the fragments and the assignment of the appropriate structures to each configuration. The energy as a function of the carbon—carbon distance is shown in Figure 3. At a distance of 6—7 a.u. an energy barrier appears. This is not unexpected, since the recoupling would need the excitation of each fragment to the first $^4\Sigma^-$ state. The barrier height is, however, much less than such excitation energy. When the distance is short enough each fragment feels the presence of the other one and there is a co-operation in the recoupling process. This is clearly evident from the results for the occupation numbers of different configurations at various distances. The contribution to the wave function from configurations that are predominant at large distance, with only two unpaired spins, practically disappears on approaching the equilibrium distance in acetylene, when only structures suitable to describe the triple bond give a substantial contribution. The change occurs in a rather abrupt way and just in the range of distances where the energy barrier is located. Since a rather limited basis set was used, only 65% of the experimental dissociation energy was retrieved. More recently a large scale MC–CI calculation on the same system has been performed.[5] Up to 178 000 configurations have been included, and the geometry and dissociation energy of acetylene reproduced almost perfectly the corresponding experimental values. The barrier along the collinear dissociation path predicted by us was recovered, at about the same internuclear distance. The quantitative aspect of the results from the large computation is substantially improved, but the qualitative behaviour of the system was correctly predicted in the former calculation, where only 22 structures were included. The enormous difference in the size of the two computations suggests a corresponding saving in computing time, and it points out that the V.B. wave function is much more easy to read and that the interpretation of results on physical and chemical grounds becomes straightforward.

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[5] P. E. M. Siegbahn, *J. Chem. Phys.*, 1981, **75**, 2314.

Before leaving the appliction of V.B. theory to reactivity I would like to mention a curiosity. It is known that catenanes, molecules in which two or more rings are linked in a chain, can be synthesized in a few examples, but at extremely low yields.[6] It has been asked if they could possibly be produced by a physical process in which one ring, carrying an electric charge and amenable to acceleration by a strong electric field, hits a second ring and a catenane is formed *via* bond–bond crossing without bond breaking. Calculations on model systems such as $H_2 + H_2$ and $H_2 + H_2^+$ were performed[7] to explore the possibility of such crossing. Potential energy surfaces of the London–Eyring–Polanyi–Sato type were built, and trajectories were calculated on such surfaces. The result was that although most trajectories led to the breaking of one or both molecules into atoms or to repulsion, in a few examples, when both molecules were in vibrationally excited states and the roto-vibrational phases at the encounter were favourable, bond crossing occurred. The chances of such events occurring, however, are so small that the process does not seem promising for practical applications.

The examples given so far employ calculation of the energy profile along least-motion paths. This path does not necessarily coincide with the least-energy path. A clear example is given in Figure 4 where the least energy path for the approach of two $^1CH_2$ groups to form ethylene as obtained by a MO–SCF–STO–3G

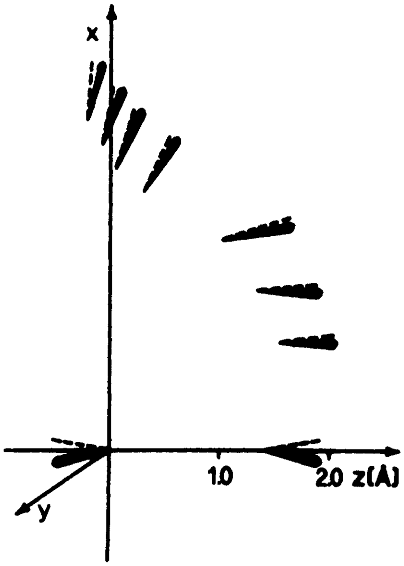

Figure 4 *Free motion approach of* $^1CH_2$ *to form ethylene*

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[6] G. Shill, 'Catenanes, rotaxanes, and knots', 1971, Academic Press, New York.

[7] G. F. Tantardini, M. Raimondi, and M. Simonetta, *Chem. Phys. Lett.*, 1974, **29**, 174.

calculation is shown.[8] No barrier was found along this path, in sharp contrast with the presence of a high barrier along the least-motion path.

Sometimes the theoretical approach is used to obtain information about the existence, stability, and structure of possible reaction intermediates. Long ago protonated methane CH_5^+ was found to exist in super-acidic media[9] and its energy and structure have been calculated. The first calculation[10] was carried on at a rather primitive level (CNDO/2); however, most accurate calculations[11] have confirmed the structure initially proposed, namely a structure showing C_s symmetry with a three-centre, two-electron bond. Three C—H distances are somewhat larger than the same distance in CH_4, and two are considerably larger. Olah has suggested that diprotonated methane CH_6^{2+} might exist and a structure with two three-centre, two-electron bonds was suggested (Figure 5). Molecular orbital calculations using a large basis set and including electron correlation *via* a perturbation treatment[12] have confirmed the existence of such a minimum. The geometry is in accord with expectation, and the force-constant matrix has no negative eigenvalues. Similar calculations[13] predicted the stability of the ethane di-cation $C_2H_6^{2+}$ [13] and it was a great pleasure to see later in the literature that this species was found in a mass-spectrometer experiment.[14]

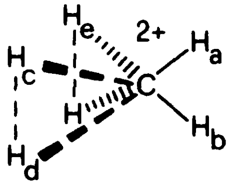
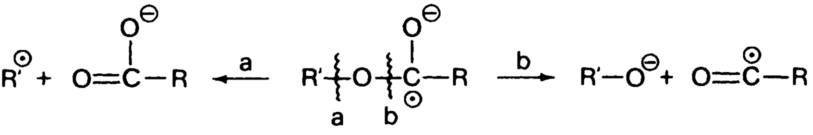


Figure 5 *Stable geometry for* CH_6^{2+}

A most interesting problem was posed by the finding that in dissolving-metal reduction of carboxylic esters, deoxygenation of the corresponding radical anions was the principal reaction,[15] while regeneration of the parent alcohol was also occurring. The two processes are indicated in Scheme 1.



Scheme 1

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[8] P. Cremaschi and M. Simonetta, *J. Chem. Soc., Faraday Transactions 2*, 1974, **70**, 1801.

[9] G. Olah, G. A. Klopman, and R. H. Schlosberg, *J. Am. Chem. Soc.*, 1969, **91**, 3261.

[10] A. Gamba, G. Morosi, and M. Simonetta, *Chem. Phys. Lett.*, 1969, **3**, 20.

[11] K. Raghavachari, R. A. Whiteside, J. A. Pople, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1981, **103**, 5649.

[12] K. Lammertsma, G. A. Olah, M. Barzaghi, and M. Simonetta, *J. Am. Chem. Soc.*, 1982, **104**, 6851.

[13] G. A. Olah and M. Simonetta, *J. Am. Chem. Soc.*, 1982, **104**, 330.

[14] D. Stahl and F. Maquin, *Chimia*, 1983, **37**, 87.

[15] A. G. M. Barrett, C. R. A. Godfrey, D. M. Holinshead, P. A. Prokopion, D. H. R. Barton, R. B. Boar, L. Foukhadaz, J. F. McGhie, and S. C. Misra, *J. Chem. Soc., Perkin 1*, 1981, 1501.

Ab initio M.O. calculations for a model parent-radical anion (namely $HCOOCH_3^{\cdot -}$) and for the fragments[16] indicated that process *a* is thermodynamically favoured by 75.6 kcal/mole, the $CH_3^{\cdot}$ + $HCOO^-$ species being more stable than the starting radical anion by 38.9 kcal/mole. It seems hard to justify the formation of alcohol, even in parts per million. The discrepancy is due to the fact that the formation of alcohol obtains by the participation of a nucleophile, the complexity of the mechanism making the results of the model calculation inapplicable. It can be inferred that the first rule in the theoretical approach to the study of reaction paths is to avoid making calculations for the wrong mechanism: in particular, special care must be taken when isolated molecule calculations are used for reactions occurring in solution.

The formation of ion-pairs may be another source of problems in solution chemistry. *Ab initio* M.O. calculations for the rotation of the CH_2 group in an allyl anion[17] have indicated an energy barrier of 22.8 kcal/mole. There is no experimental measure of the rotational barrier of the free allyl anion. Only $C_3H_5^-Me^+$ ion-pairs in THF have been studied: the following values of $\Delta G^{\neq}$ were reported (kcal/mole)[18]: 10.7 for Li^+, 16.7 for K^+, and 18.0 for Cs^+. From these data it was deduced that the rotational barrier for the isolated anion cannot be smaller than 18 kcal/mole. A better estimate of the barrier in the free anion can be deduced by evaluation of anion–cation interaction. The influence of the solvent should be negligible, since we are dealing with tight ion-pairs. In the case of caesium cation the distance from the anion is such that the interaction energy can be approximated from the electrostatic contribution alone,[19] that can be evaluated on the maps of the molecular electrostatic potential.[20] The result is that cation–anion interaction energy is constant along the CH_2 rotation and the value of 18 kcal/mole is a reliable estimate of the barrier height for the free anion.

Less elaborate computational schemes can be of value in particular cases. One example is the geometrical and optical isomerization in substituted cyclopropanes. The proposed mechanism for such reactions is the rupture of one carbon–carbon bond in the ring, followed by rotation of one or both terminal CXY groups and ring re-closure. Doering and Sachdev[21] made very accurate measurements of rate constants for *cis* and *trans* 1-cyano-2-isopropenylcyclopropane. An approximate evaluation of the barrier to single and double rotation in cyclopropane itself has been made by Hoffmann[22] who used the extended Hückel method (EH). The same procedure was applied to mono- and di-substituted derivatives.[23] The following conclusions were drawn: (a) the rate of reactivity increases in the order cyclopropane < monosubstituted cyclopropane < disubstituted cyclopropane; (b) in monosubstituted rings the breaking of the bond adjacent to the substituent

[16] P. Cremaschi, G. Morosi, and M. Simonetta, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 673.

[17] P. Cremaschi, G. Morosi, and M. Simonetta, *J. Mol. Mol. Struct.*, 1981, **85**, 397.

[18] T. B. Thompson and W. T. F. Ford, *J. Am. Chem. Soc.*, 1979, **101**, 5459.

[19] M. Simonetta, *Int. Rev. Phys. Chem.*, 1981, **1**, 31.

[20] E. Scrocco and J. Tomasi in 'Advances in Quantum Chemistry', Vol. 11, ed. P. O. Lowdin, 1978, Academic Press, New York.

[21] W. von E. Doering and K. Sachdev, *J. Am. Chem. Soc.*, 1979, **96**, 1169.

[22] R. Hoffmann, *J. Am. Chem. Soc.*, 1968, **90**, 1975.

[23] A. Gavezzotti and M. Simonetta, *Tetrahedron Lett.*, 1975, **97**, 4155.

is the most favourable process; (c) double rotation is favoured over single rotation in unsubstituted cyclopropane, in phenyl and isopropenyl derivatives; in the cyano-derivative the two processes should be competitive; (d) in Doering's compound only the most heavily substituted bond breaks, and the order of reactivity should be; *trans* (isopropenyl) < *trans* (CN) < *trans* (both) < *cis* (isopropenyl) < *cis* (CN) < *cis* (both) where the parentheses include the rotating groups. The agreement with experimental results is excellent. One more compound has been considered, namely *cis*- and *trans*-1,2-dicyanocyclopropane.[24] In this molecule the preference for double rotation is so strong that geometrical isomerization should obtain *via* rupture of one of the bonds stemming from the CH_2 group. This result still waits for experimental verification.

The Cope reaction is a thermal intramolecular rearrangement that obtains in diallylic systems (Scheme 2).

$$\mathrm{A{=}B{-}C{-}D{-}E{=}F} \longrightarrow \mathrm{C{=}B{-}A{-}F{-}E{=}D}$$

Scheme 2

A completely empirical method, molecular mechanics,[25] was used to study the reaction path. For the activated complex both a boat-like and a chair-like geometry are in competition (Figure 6). In the case of hexa-1,5-diene the chair-like nature of the activated complex has been demonstrated.[26] When a ring is welded on the central bond C—D, as in 1,2-*cis*-divinylcyclopropane or 1,2-*cis*-divinylcyclobutane only the boat-like route is available. The energy and the geometry of transition states in these reactions have been evaluated, and the results compared with experimental values. The agreement was excellent for hexadiene and the butane derivative.[27] For the cyclopropane derivative no data were available, however, since this molecule had not been synthesized. Only a few years later the compound became available and its behaviour in the rearrangement was studied

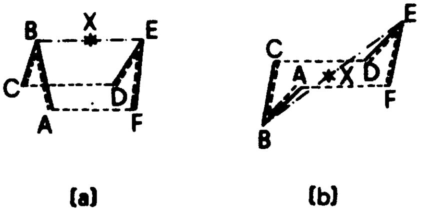

Figure 6 *Transition states for the Cope rearrangement: (a) boat-like, (b) chair-like*

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[24] M. Simonetta and A. Gavezzotti, *Atti. Accad. Sci., Torino*, 1977, **111**, 93.

[25] J. A. Williams, J. Stang, and P. v. R. Schleyer, *Ann. Rev. Phys. Chem.*, 1968, Vol. 18, p. 531.

[26] W. von E. Doering and W. Roth, *Tetrahedron*, 1962, **18**, 67.

[27] M. Simonetta, G. Favini, C. Mariani, and P. Gramaccioni, *J. Am. Chem. Soc.*, 1968, **90**, 1280.

and found to correspond well with our prediction:[28] $\Delta H^{\neq}$ (kcal/mole) = 17.2 (calc.), 19.4 (exp.); $\Delta S^{\neq}$ (273 °C e.u) = − 5.5 (calc.), − 5.3 (exp.).

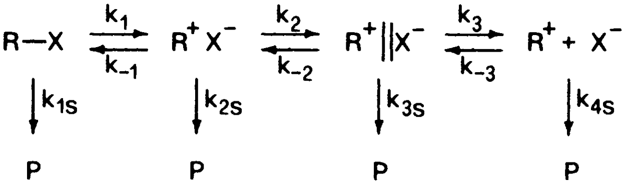
A similar approach was used in the study of the interconversion path in 1,1′-dimethyl-9,9′-bifluorenylidene.[29] For rotation around the central bond in the parent compound, molecular mechanics calculated a very low rotational barrier, 2.8 kcal/mole, as expected, since n.m.r. spectra for this compound show no temperature dependence.

However, for the dimethyl derivative we found a barrier of 18.7 kcal/mole on the path from the twisted conformation of the *E*-isomer, to the folded conformation of the *Z*-isomer. From dynamic n.m.r. spectra of this compound a $\Delta G^{\neq}$ (382 K) = 19 kcal/mole was deduced:[30] the agreement is as good as can be expected.

3 Solvation Effects

Most organic reactions are carried out in solution and in many instances calculations for the isolated molecules do not lead to results than can be used in connection with real chemistry since the influence of the solvent on reaction mechanism and products can be so strong that any comparison becomes meaningless. We have already seen one such case in the reduction of carboxylic-ester radical anions.

In order to investigate reactions in solution an appropriate model must be constructed. This can be done in many different ways. We present here the model we have been using for many years. Calculations are performed for a supermolecule made of the reactant molecule plus a suitable number of solvent molecules to reproduce the first solvation shell. Even in simplest situations the number of degrees of freedom to be dealt with is very large, an approximate method of calculation must be considered and particular attention must be given to the energy minimization procedure. The first reaction to be mentioned here is the dissociation (and subsequent solvolysis) of alkyl halides in polar solvents. A large body of experimental studies for this reaction was produced by Winstein,[31] leading to the formulation of Scheme 3.



Scheme 3

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[28] J. M. Brown, B. T. Golding, and J. Stofko, jun., *J. Chem. Soc., Chem. Commun.*, 1973, 319.

[29] G. Favini, M. Simonetta, M. Sottocormola, and R. Todeschini, *J. Comput. Chem.*, 1982, 3, 175.

[30] I. Agranat, M. Rabinovitz, A. Weitzen-Dagan, and I. Gosnay, *J. Chem. Soc., Chem. Comun.*, 1972, 732.

[31] S. Winstein, 'Chimica Teorica', ed. M. Simonetta, Acc. Naz. Lincei, Roma, 1965.

In the theoretical approach, fluoromethane in water was chosen: the smallest alkyl halide required the least number of solvent molecules to build the first solvation shell. The method of calculation used was M.O. theory at the CNDO/2 level, since the applicability of such a method to the study of solvation problems had been tested in different areas and on different systems[32] with satisfactory results. The solvation of separated CH_3^+ and F^- ions was studied first, to find that 5 and 6 water molecules must be included in the first solvation shell, respectively. For the reactant CH_3F, eleven water molecules were then considered. The energy of the system $CH_3F,11H_2O$ was calculated for increasing values of the $C \cdots F$ distance, allowing the rigid H_2O molecules to choose their positions in the surrounding space.[33] The dissociation curve for CH_3F *in vacuo* was also calculated by the same method.[34]

The results are shown in Figures 7 and 8 respectively. While CH_3F dissociates monotonically in the gas phase, three minima are found in solution.

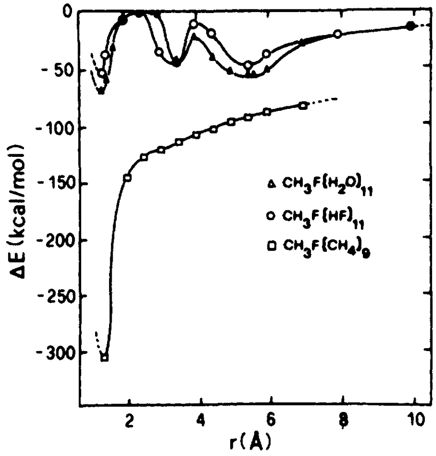

Figure 7 *Energy curves for dissociaiton of* CH_3F *in water, hydrofluoric acid, and methane*

The geometrical features corresponding to each minimum in the solvated system suggest the following definitions: the first minimum is undissociated CH_3F dissolved in water and hence slightly relaxed (C—F distance = 1.38 Å in H_2O, 1.31 Å *in vacuo*), the second minimum is an intimate ion-pair ($C \cdots F$ = 3.48 Å) with the O—H bond of two water molecules parallel to the C—F internuclear line, and the third minimum ($C \cdots F$ = 5.46 Å) is a pair of dissociated CH_3^+ and F^- ions, each surrounded by its own solvent shell. The same three minima were obtained starting from a number of different points in the hyperspace and changing the order of

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[32] P. Cremaschi, A. Gamba, and M. Simonetta, *Theor. Chim. Acta.*, 1972, **25**, 237 and 1973, **31**, 155; P. Cremaschi and M. Simonetta, *Theor. Chim. Acta.*, 1975, **37**, 341.

[33] P. Cremaschi, A. Gamba, and M. Simonetta, *J. Chem. Soc., Perkin Trans. 2*, 1977, 162.

[34] P. Demontis, E. S. Fois, A. Gamba, B. Manunza, G. B. Suffritti, and M. Simonetta, *J. Mol. Struct., Teochem.*, 1983, **93**, 231.

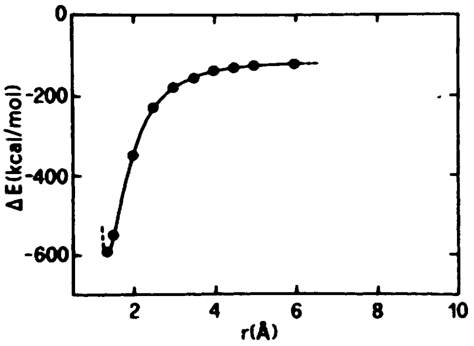

Figure 8 *Energy curve for dissociation of* CH_3F *in vacuo*

optimization of the geometrical parameters. The possibility that the result might depend on minima in the solvent–solvent interaction energy could be excluded since the minima are stable when such energy is subtracted from the total energy. The effect of changing to another polar solvent was tested by substituting HF for H_2O.[35] The shape of the energy curve is slightly affected (Figure 7). If a non-polar solvent is used, such as CH_4, then ion-pairs disappear and a curve similar to the one found *in vacuo* is obtained (Figure 7). To further confirm the results from semi-empirical calculations, the dissociation of CH_3F in HF (the smallest one among our systems) was studied also by an *ab initio* method, namely SCFMO at the STO 3G level.[36] The shape of the dissociation curve is preserved and so are the three minima.

Once the influence of the solvent had been investigated, the next step was to determine the effect of change of solute. The necessary experimental background was available for the dissociation of substituted benzenediazonium cations in fluorinated solvents:[37] in the de-diazoniation reaction evidence for the formation of ion-molecule pairs was claimed. Calculations similar to those used in the previous system, using benzenediazonium cation as substrate and water as the solvent, confirmed the multi-minima behaviour of the dissociation curve.[38] When methanediazonium cation in water was investigated, the calculations showed that de-diazoniation occurs without formation of intermediates though the dissociation energy is drastically reduced on going from gas phase to solution,[39] as shown in Figure 9. From the same figure it can be seen that the behaviour in HF closely follows that found in water.[35] It was a pleasure to discover that the kinetics and

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[35] P. Demontis, E. S. Fois, A. Gamba, B. Manunza, G. B. Suffritti, and M. Simonetta, *J. Chem. Soc., Perkin Trans. 2*, 1982, 783.

[36] A. Gamba, B. Manunza, C. Gatti, and M. Simonetta, *Theor. Chim. Acta.*, 1983, **63**, 245.

[37] I. Szele and H. Zollinger, *J. Am. Chem. Soc.*, 1978, **100**, 2811; Y. Hashida, R. G. M. Landells, G. E. Lewis, I. Szele, and H. Zollinger, *J. Am. Chem. Soc.*, 1978, **100**, 2816.

[38] A. Gamba, M. Simonetta, G. Suffritti, I. Szele, and H. Zollinger, *J. Chem. Soc. Perkin Trans. 2*, 1980, 493.

[39] P. Demontis, R. Ercoli, A. Gamba, G. B. Suffritti, and M. Simonetta, *J. Chem. Soc., Perkin Trans. 2*, 1981, 488.

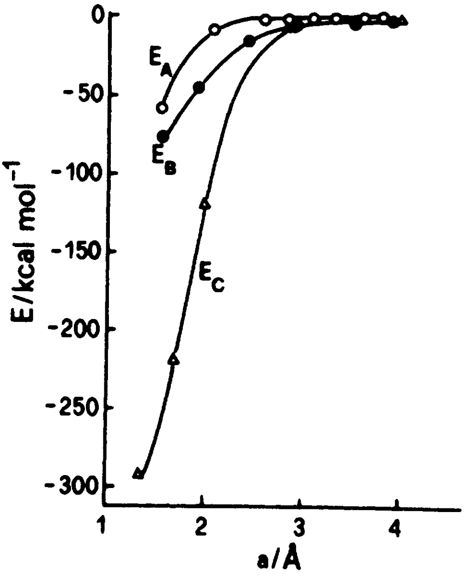

Figure 9 *Energy curve for dissociation of* $CH_3N_2^+$: *A, in* HF; *B, in* H_2O; *C, in vacuo*

mechanism of hydrolysis of diazomethane in a THF–water mixture have shown that no intermediates are found in the nucleophilic attack of the methanediazonium ion.[40] Since an opposite behaviour was found for the benzene and the methane derivatives, a natural extension was the investigation of the de-diazoniation of vinyldiazonium cation in water.[41] As might perhaps be expected, this ion behaves like the benzene derivative and the formation of ion-molecule pairs is predicted. Unfortunately, no experimental evidence to support or to contradict this prediction is available.

From the body of the above results it can be inferred that, though the model is oversimplified and the technique for calculation rather primitive, the formation of ion pairs in solvolytic and de-diazoniation reactions of appropriate substrates in polar solvents is clearly established on theoretical grounds. It is gratifying that different authors using a completely independent method of calculation have reached the same conclusion.[42]

4 Reactions in the Solid State

Solid state reactivity is an interesting but rather complicated subject since reactivity in crystals depends on a balance between steric factors and electronic properties. As a consequence, usual quantum mechanical methods are not sufficient to

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[40] J. F. McGarrity and T. Smyth, *J. Am. Chem. Soc.*, 1980, **102**, 7303.

[41] E. Fois, A. Gamba, M. Simonetta, I. Szele, and H. Zollinger, *J. Phys. Chem.*, 1982, **86**, 3722.

[42] L. Salem, 'Electrons in Chemical Reactions', J. Wiley, New York. 1982, p. 240.

investigate reactions in organic crystals. They must be substituted or supplemented by empirical calculations of intermolecular forces. Such empirical methods have been developed mainly to study motions in the solid state, such as thermal librations, re-orientations, phase transitions and reactions.[43] The most usual reactions in organic crystals are photochemical reactions. These are more open to experimental studies than to the theoretical approach, since empirical methods have been calibrated on properties of molecules in the ground state, and it is known that a satisfactory quantum mechanical description of excited states is a difficult goal.

Among the few well known reactions let me mention the rearrangement of methyl dimethylaminobenzenesulphonate (DMABS) to give the corresponding zwitterion:

$$(CH_3)_2N{-}C_6H_4{-}SO_3{-}CH_3 \longrightarrow (CH_3)_3{-}N^+{-}C_6H_4{-}SO_3^- \qquad (4)$$

The reaction is faster in the solid state than in solution or in the melt.[44] The crystal structure determination has shown that, in the crystal, molecules are arranged in sheets, with an almost perfect orientation for the methyl transfer reaction to occur. The reaction was proved to be intermolecular and this is confirmed by non-bonded interaction calculation.[45] Transfer of a methyl group from one end to the opposite one in the same molecule would involve an unacceptable non-bonded energy barrier: the methyl group would crash against the surrounding molecules. The intermolecular reaction was studied by considering methyl group migration from one molecule to the next one; the energy of the system $(CH_3)_2{-}C_6H_4{-}SO_3{-}CH_3 + CH_3^+$ was calculated by the EH technique as a function of two parameters, the distance of an incoming methyl carbon from the nitrogen atoms and the distance of a leaving methyl carbon from the oxygen. The potential surface is similar to that expected for a $X + YZ = XY + Z$ reaction, but instead of a saddle a minimum was found. Crystal field potential energy calculations were also carried out, to show that pyramidalization of the $N(CH_3)_2$ group in the direction opposite to the incoming CH_3^+ group obtains at practically zero energy cost, while the migrating CH_3^+ group (where H atoms have to move faster than the C atoms as a result of inversion) interacting with the surrounding molecules experiences a barrier of just a few kcal/mole. Since experiments had shown the reaction to occur in two steps, the nature of the intermediate was elucidated (a molecule–ion pair) and the enhancement of the reaction rate in the crystal could be attributed to the favourable entropic factor arising from the appropriate orientation of the reacting molecules.

An interesting new approach to the study of solid-state reactivity was recently proposed,[46] based on the evaluation of the volume of cavities within the crystal. When applied to DMABS, the presence of a cavity in the region of the migrating methyl was found. The maps in Figure 10 show values of D_i for different sections

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[43] A. Gavezzotti and M. Simonetta, *Chem. Rev.*, 1982, **82**, 1.

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[46] A. Gavezzotti, *J. Am. Chem. Soc.*, 1983, **105**, in the press.

of the unit cell. D_i is defined as $\frac{N_{\mathrm{occ}}}{N}$, that is the ratio of the numbers of vectors that fall in an occupied region of space to the total number of trial vectors for each portion V_i of the unit cell. Typical values of V_i are 0.2—0.5 Å^3 and the density of trial points is of the order of $1000/\text{Å}^3$. V_i is occupied when $D_i > 0.4$, empty for $D_i < 0.1$. From Figure 10 it is clear that the crystal offers appropriate cavities to make the reaction possible. To close I want to mention that recently another reaction has been discovered to occur more rapidly in the solid state then in the melt, namely dimerization of 4,4′-methylene bis(phenylisocyanate) ($O{=}C{=}N{-}C_6H_4{-}CH_2{-}C_6H_4{-}N{=}C{=}O$).[47] Again the arrangement of the molecules in the crystal is such as to favour the reaction leading to the dimeric azetidione. Evaluation of cavities allows a rationalization of these findings.

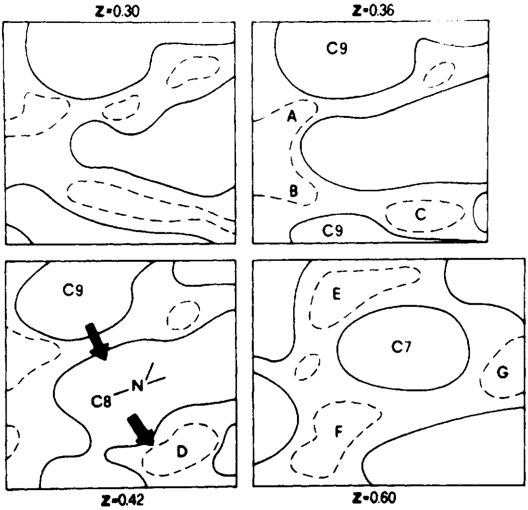

Figure 10 *Sections of the D_i map for DMABS crystal at different z levels (z in fractional cell units). Arrows mark displacements of the reacting methyl groups. The dashed curves enclose zones with $D_i < 0.10$ and full lines enclose zones with $D_i > 0.7$*

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[47] R. B. Wilson, Y. Chen, I. C. Paul, and D. Y. Curtin, *J. Am. Chem.*, 1983, **105**, 1672.