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Gradient lines on multidimensional potential energy surfaces and chemical reaction mechanisms

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Abstract. We show that the path of a chemical reaction on the potential energy surface of a chemical system can only be a gradient line between two critical points. Existing rules of symmetry conservation along the reaction path are analysed to establish their consistence with published experimental data and with ab initio calculations. In some systems the possible existence of reaction paths consisting of several gradient lines (both equivalent and nonequivalent) has been demonstrated. The relationship between the reaction mechanisms and the corresponding paths on the potential energy surface is discussed. The bibliography includes 238 references.

I. Introduction

The dynamics of chemical reactions on the appropriate potential energy surfaces (PES) are currently being studied in depth.[1–4] However, many problems relating to the structure of the PES and to the paths of chemical reactions on this surface are still controversial,[4–7] and in many cases have not yet been clearly and precisely formulated. Thus, studies of the dynamics of the thermo- and phototransformation of molecules (both in a gas and in a condensed medium) require a correct definition of the topology of the PES for both the ground and the excited state, as well as of their relative disposition over a reasonably wide range of changes in the intrinsic coordinates. Currently used one-dimensional models of various photoprocesses are far from offering a solution of these problems. A good example is provided by a study[8] of the dynamics of the photochromic behaviour of the indoline spiropyran **1** (1′,3′,3′-trimethyl-6-hydroxyspiro[2*H*-1-benzopyran]2,2′-indoline) in solution by nano- and femtosecond spectroscopy methods (Fig. 1). When the compound **1** is irradiated ($\lambda \approx 300$ nm) the C–O bond breaks in less than 100 fs with formation of the metastable compound **2**, which then isomerises to the merocyanine form **3**. The whole process is represented schematically by a one-dimensional energy diagram. This model cannot account for the many motions of a chemical system as complex as molecule **1** on the multidimensional surface of the ground and the excited state.

The dynamic behaviour of chemical systems in the classical or the quantum approximation is now being studied mainly in the one-channel approximation, although many examples of reactions taking place along several equivalent paths are

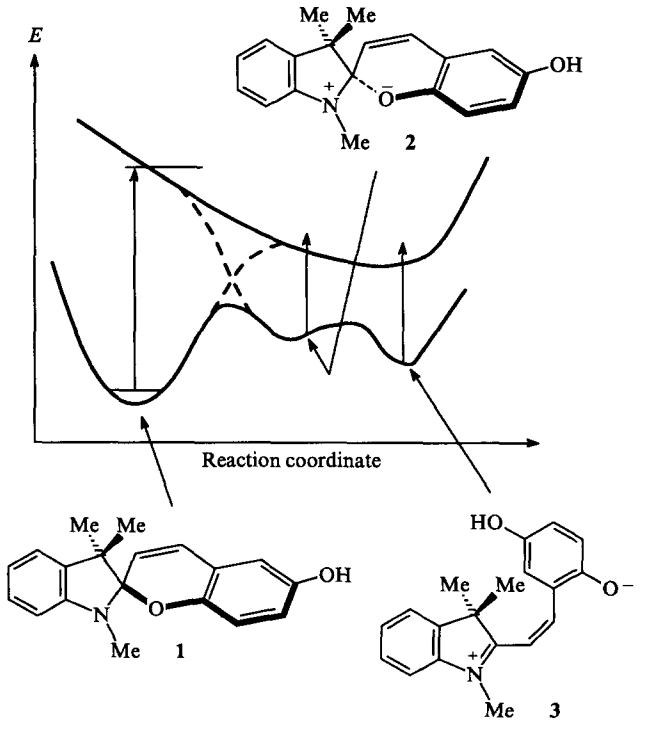


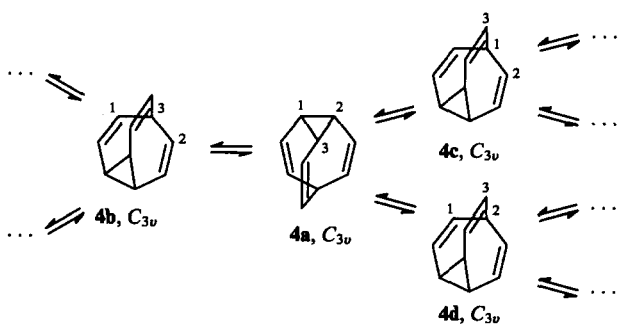
Figure 1. Scheme of the photochemical opening of 1′,3′,3′-trimethyl-6-hydroxyspiro[2*H*-1-benzopyran]-2,2′-indoline (**1**) (see Ref. 8). (**2**) initial metastable product, corresponding to the structure with a broken C–O bond but retaining the configuration of the fragments lying in perpendicular planes; (**3**) merocyanine form, which follows the reac-tion path along the diabatic surfaces (broken lines). Only one of the vari-ous possible merocyanine isomers (**3**) is shown in the figure as a product.

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known,[9-22] for example the isomerisation of bulvalene **4** (Scheme 1),[9-12] the internal rotation of two or several groups in various systems,[13-19] the opening of cyclopropane[20,21] and ozone rings,[22] and other systems.[23-25] Clearly, changing to a multichannel representation of the reaction dynamics requires the development of new approaches to the description and the treatment of the PES, and also to the study of the system dynamics on such a surface.

Scheme 1



As shown by recent work,[26-37] the effect of a solvent on the mechanism and rate of the reaction is not so much a static effect as the effect of the direct participation of one or several solvent molecules in the reaction as discrete species. This undoubtedly requires the inclusion of the solvent molecules into the PES being considered for the chemical systems.

Studies of the structure of a solid surface,[38] of its interaction with adsorbed molecules, and of the chemical reactions taking place on the surface are impossible without a detailed knowledge of the structure of the PES for a combined system consisting of the adsorbed molecule and a model of the solid surface.[38-45] Configurational transitions of the solid from one symmetry group to another can be treated as transitions from one minimum to another in the appropriate PES.

The development of molecular devices for use in molecular electronics is greatly dependent on studies of the complex motion of the chemical system along the appropriate PES.[46,47] The problem of the transformation of one form of energy into another is far from solved,[48,49] and therefore studies of the direct molecular conversions of solar energy are important.[49-52] The search for molecular systems capable of storing solar energy, concentrating it, and converting it into forms convenient for practical applications relies on the study of the structure of the adiabatic PES of the appropriate chemical systems.[49]

A deeper understanding of the nature of biological systems and of their operating principles obviously requires a detailed study of the PES of model chemical systems simulating the totality of active centres and their collective properties.[53-56]

It follows from the above considerations that the study of the global PES is only beginning. The solution of many key theoretical and experimental problems is associated most closely with the study of the structure of the appropriate PES.

With the exception of the report by Bazilevskii and Ryaboi[4] there have so far been no reviews of the problems associated with the global structure of the PES in the Russian literature. Therefore the main aim of the present paper will be to fill this gap by stressing the many examples of inadequate studies of the PES, and thus to promote a wider understanding of the reaction path.

II. Path of a chemical reaction on the potential energy surface

The path of a chemical reaction on the PES,[57-59] which determines its mechanism, is one of the most important concepts in chemistry. This concept, first introduced[57] in the late 1930s immediately following the establishment of the concept of an adiabatic PES for the molecule,[60] is still controversial.[4-7,61-77] There are several different definitions of the reaction path, of which the most important are the minimum energy reaction path,[57-59,71-73] the path of steepest descent,[67-69,72,76] and the intrinsic reaction coordinate.[61,63,68]

The minimum energy path (MEP) is a line following the bottom of the reaction valley and connecting the energy minima of the reactants and products through the appropriate saddle point (transition state[78,79]) on the PES. The path of steepest descent is a gradient line originating at the saddle point and pointing towards the energy minima of the reactants or of the products. When mass-weighted coordinates are used the path of steepest descent becomes the intrinsic reaction coordinate (IRC).[61,63,68] In the construction of a topological PES structure, when the reaction valley connects the energy minima of reactants and products through a high saddle, all the above definitions of the reaction path are described by the same line on the PES (Fig. 2). In more complex topological structures of the PES the minimum energy path, the gradient line, and the IRC can be different, and therefore the mechanisms predicted for a given reaction may also differ. Of course, it becomes essential to choose the definition of the reaction path on the PES which is most appropriate to the physics and chemistry of the process being studied. Without denying the possible validity of the MEP or of the IRC this review will be concerned mainly with the gradient reaction path.[7,80] The choice of this definition of the path is most convenient in the case of a PES having a complex topological structure. We shall discuss only the PES of the electronic ground state, although the methodology developed in this review is equally applicable to the PES of any electronic state.

The potential energy surface $E(X)$ and its first and second derivatives are assumed to be finite and continuous functions at any point X (X_1, X_2, ..., X_{3N}) of the configurational space R^{3N} except at the poles (the points where the coordinates of two or more atoms in the molecule coincide). The chemically most important regions of the PES are the so-called nondegenerate critical (stationary or extremal) points, i.e. the points X_{cr} on the PES where the following relationships are satisfied simultaneously;

$$\nabla E(X_{cr}) = \operatorname{grad} E(X_{cr}) = 0\,, \tag{1}$$

$$\operatorname{rank}(H_{ij})_{X_{cr}} = \operatorname{rank}\left\|\frac{\partial^2 E}{\partial X_i \partial X_j}\right\|_{X_{cr}} = 3N-6\,, \tag{2}$$

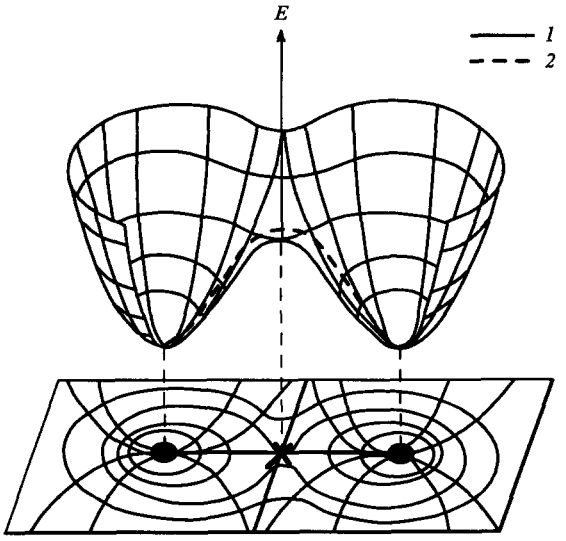


Figure 2. Potential energy surface of the molecule and its two-dimensional projection on the configurational space. (*1*) Path of the reaction on the PES, (*2*) projection of the reaction path on the configurational space. The curves emerging from the minima are gradient lines, the closed curves are equipotential lines.

where X and N are (respectively) the Cartesian coordinates of the nuclei and the number of atoms in the molecule.[64,65,78,79] Eqn (2) states that the Hessian (H_{ij}) has only six zero eigenvalues corresponding to the motion of the molecular system as a whole (three translations with respect to the three axes and three rotations round these same axes).

The point $X \in R^{3N}$, where the relationship (1) is not obeyed [$\nabla E(X) \neq 0$], is called a regular[81,82] (noncritical or normal[61,65]) point. All the critical points are characterised by the index λ (the number of negative eigenvalues of the Hessian). Thus, for a minimum $\lambda = 0$, for a saddle point $\lambda = 1$, for a critical point $\lambda = 2$, etc.[65]

The reaction path of the chemical system[57-59,61,83] is defined by a line on the PES which originates from the energy minimum for the reactant, passes through the saddle point corresponding to the transition state, and terminates at the energy minimum for the product (see line *1* of Fig. 2). The reaction path is defined in $(3N+1)$-dimensional R^{3N+1} space (the direct sum of the configurational space and of the energy coordinate $R^{3N+1} = R^{3N} \oplus E$),[81] which we shall call the entire space. A mutually single-valued correspondence exists between the points (and therefore also the curves) on the PES and in the configurational space. Thus the line in the configurational space directly defines the line on the PES, and vice versa. The orthogonal projection of the reaction path on the configurational space gives a curve in the R^{3N} space which is also called the reaction path (see line *2* in Fig. 2). We shall in most cases refer to the reaction path in the entire space.

In the adiabatic approximation[60] the PES is independent of the nuclear masses, and therefore any lines lying on the PES and its projection on the R^{3N} space are also independent of the nuclear masses. An infinitesimally small displacement along the PES from any point X_0 (produced by motion at an infinitesimally small speed) can only follow the direction of the gradient vector.[61,67,69] The result is that under conditions of infinitesimally small displacement the molecular system can slide on the PES only along the gradient lines between any two critical points.[61,63,68,69] Therefore of all the lines on the PES only the gradient line can act as the reaction path. In this case in order to identify the line on the PES corresponding to the path of the chemical reaction we must solve a system of ordinary differential equations defining the gradient lines on the PES, which can be written in Cartesian coordinates not weighed for mass in the well-known form,[61,63,68,81,82]

$$\frac{dX_1}{\partial E/\partial X_1} = \frac{dX_2}{\partial E/\partial X_2} = \cdots = \frac{dX_{3N}}{\partial E/\partial X_{3N}} = \text{const}, \qquad (3)$$

with the initial conditions $X_0 = (X_1, X_2, ..., X_{3N})_0$, and from the family of solutions of this system we must choose those which connect the appropriate critical points. Eqn (3) in mass-weighted coordinates was first used by Fukui[61] (in 1970) as a means of finding the reaction path. However, we should note that in studies of the dynamics of chemical systems it is convenient to work with mass-weighted coordinates,[61] though we shall not consider these in the present review, leaving interested readers to consult the original publications.[1-4,61,63,68]

For our purpose Eqn (3) is conveniently written as a system of $3N$ ordinary differential equations[4,61,67-69,80]

$$\frac{dX_i}{dt} = -\frac{\partial E[X_1(t), ... X_{3N}(t)]}{\partial X_i}, \quad i = 1, 2, ..., 3N, \qquad (4)$$

with the initial conditions $X(t_0) = (X_1, X_2, ..., X_{3N})_0$. The quantity t is a parameter for the length of the curve. The minus sign on the right-hand side of Eqn (4) means that the potential decreases as t increases. The integral curves of Eqn (4) are called the gradient lines $X = X(t)$ of the adiabatic potential.[68,69]

Thus under conditions of infinitesimally small displacement the molecular system can move on the PES only along gradient lines connecting any two critical points.[61,63,68] Only a gradient line can act as the reaction path among the lines belonging to the PES.

According to Ostgood's theorem[85,86] the system (4) with a right-hand side satisfying the Lipshits condition

$$\left| \frac{\partial E(X')}{\partial X_i} - \frac{\partial E(X'')}{\partial X_i} \right| \leqslant K \sum_i^{3N} |X_i' - X_i''|,$$

where X', $X'' \in R^{3N}$ and K is a positive constant, has a unique solution which passes through the given initial point X_0. Obviously the condition imposed on the PES ensure that the Lipshits conditions are obeyed by the right-hand side of (4), and therefore that for these condition the Ostgood theorem applies. Thus there is only one solution of the system (4), $X = X(t)$, which passes through the given regular point.[69,70,80,85,86] This means that the gradient line can neither disappear at nor emerge from a regular point, i.e. that gradient lines can have no bifurcations on the slopes of the PES.

The vector-gradient field ∇E behaves like an ordinary electrostatic field, whose integral lines of force do not intersect[84] (see also the quantum topology theory[87]).

In curvilinear coordinates $Q(X) \in R^{3N-6}$ (where R^{3N-6} is the configurational space of the intrinsic coordinates) the Eqns (4) can be written in the tensor form[4,6,68,74,88]

$$\frac{dQ^k}{dt} = -\sum_{l=1}^{3N-6} g^{kl} \frac{\partial E[Q^1(t), ..., Q^{3N-6}(t)]}{dQ^l}, \qquad (5)$$

$$k = 1, 2, ..., 3N-6,$$

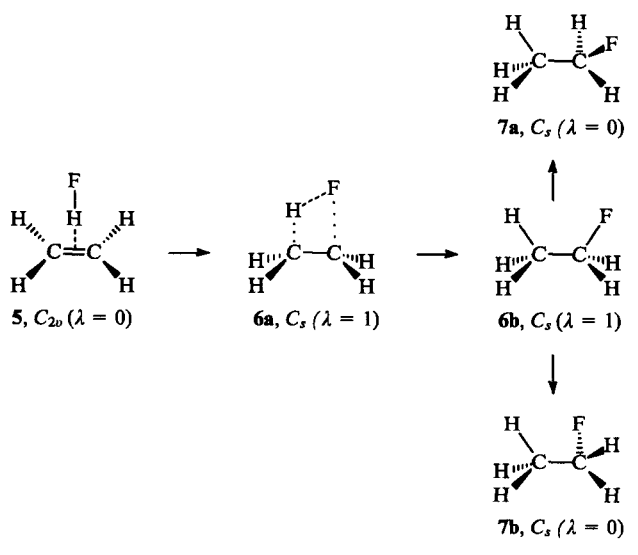
where the metric tensor g^{kl} (see Refs 81 and 88) is defined by the equation[4,74]

$$g^{kl} = \sum_{i=1}^{3N} \left[\frac{\partial Q^k}{\partial X_i}\right] \left[\frac{\partial Q^l}{\partial X_i}\right], \quad k = l = 1, 2, ..., 3N-6.$$

It is important to note that the functions $E(X)$ and $E(Q)$ define the same adiabatic PES, and the equations (4) and (5) give the same system of gradient lines.[4,6,67,74] The tensor form (5) ensures the invariance of the gradient lines for any transformation of the coordinates with a nonzero Jacobian. Thus the gradient lines, like the PES, are defined only by the given molecular system and are independent of the choice of coordinates.

A system of gradient lines connecting the energy minima of reactants and products and passing through one or several saddle points is called a gradient reaction path.[7,80] Thus in order to obtain the gradient reaction path we must have the solutions of Eqns (4) and (5), but this cannot be done in an explicit form since the functions $E(X)$ and $E(Q)$ are not known in an analytic form even

Scheme 2



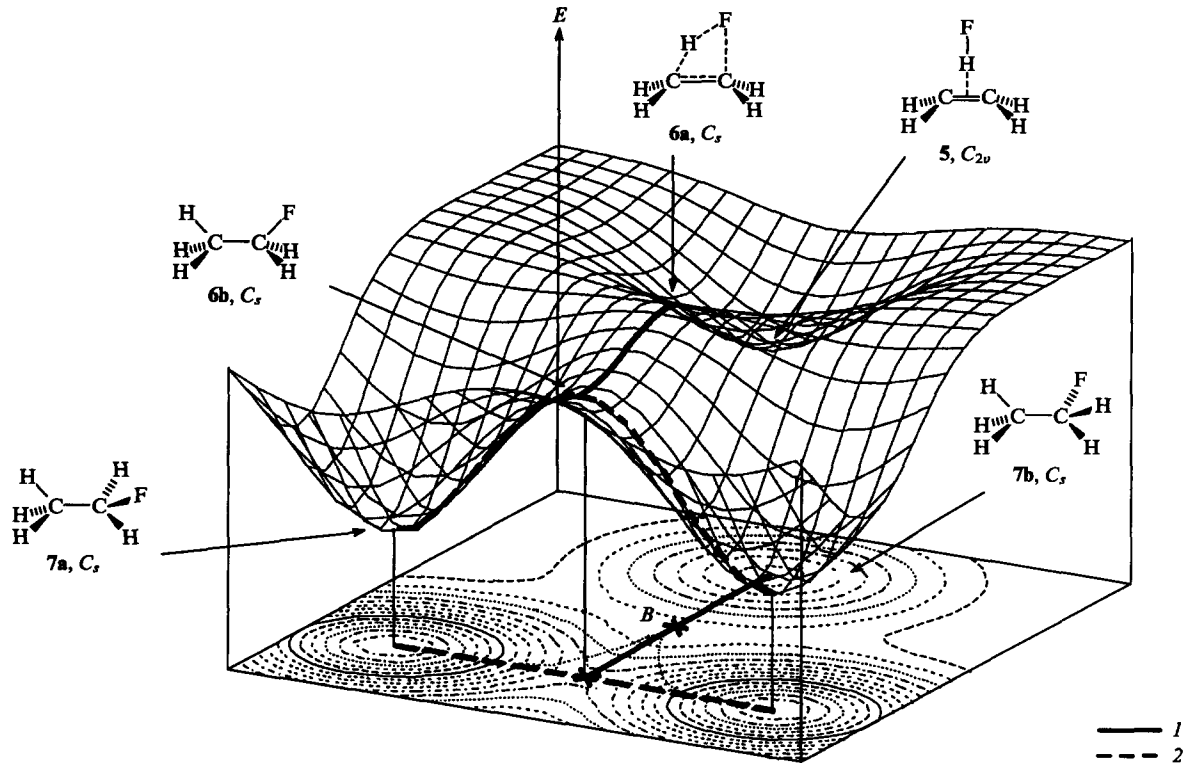


Figure 3. Potential energy surface for the electrophilic addition of HF to the C=C double bond of ethylene.[7] The line *1* corresponds to the initial part of the reaction **5** → **6a** → **6b**. The line *2* corresponds to the reaction **7a** ⇄ **6b** ⇄ **7b** for the internal rotation in the substituted ethane; the lines emerging from the bifurcation point *B* define the minimum energy path; the transition states are shown by crosses.

for the simplest triatomic systems.[71] However, numerical approximations to the gradient lines can now be obtained without great difficulty. We shall consider, as an example, the gradient path of the electrophilic addition of HF to a molecule of ethylene.[7] Nonempirical calculations (MP2/DZP) have predicted[7] that this reaction can be represented by the Scheme 2.

The structure of the PES for this reaction is shown in Fig. 3. The reaction, which begins with the formation of the metastable π-complex **5**, is described by the gradient line *1* in the region **5** → **6a** → **6b**. This line passes through the saddle point corresponding to the transition state **6a** and reaches the neighbouring saddle point corresponding to the other transition state **6b** for the internal rotation round the C–C bond.

At the point on the PES corresponding to the state **6b** the gradient path of the reaction changes direction in the configurational (entire) space and passes from the first gradient line to the second (line *2* of Fig. 3), reaching the minima of the states **7a** and **7b** along the two branches of the second line.

If the gradient line connects two critical points all the eigenvectors of the Hessian $\vec{q}_i$ of one critical point should smoothly change at the point of descent along the gradient line into the accompanying Frenet polyhedron,[81,82] which should itself be transformed into the appropriate eigenvectors of the Hessian for the other critical point.

In this case it is sufficient to consider the evolution of the two eigenvectors of the Hessian $\vec{q}_1$ and $\vec{q}_2$ along the first gradient line from the state **6a** to the state **6b** (see Fig. 4). The transition vector $\vec{q}_1$ of the state **6a** at the point of descent is converted into the tangential vector $\nabla E/|\nabla E|$ ($\vec{q}_1$ at the point *B*), which is further converted (for the state **6b**) into the eigenvector of the Hessian corresponding to the first positive eigenvalue ($\vec{q}_1$ at the point **6b**). At the same time the perpendicular vector $\vec{q}_2$, corresponding to the eigenvector of the Hessian for the first positive eigenvalue at the point **6a**, is continuously transformed along the gradient line, becoming the transition vector $\vec{q}_2$ for the structure **6b**.

Thus the gradient path of the addition of HF to ethylene consists of two nonequivalent gradient lines of which the first connects the points **5** → **6a** → **6b**, and the second the points **7a** → **6b** → **7b**. A characteristic feature of the PES is shown in Fig. 3: the first gradient line emerging from **6a** does not reach either of the minima at **7a** or **7b**. Along this gradient line and beyond the point *B* a shift in a perpendicular direction lowers the energy, i.e. a reaction valley develops beyond the bifurcation point *B* and therefore the MEP splits into two (broken lines in Fig. 3). The minimum-energy path begins at the point **6a** and leads to the minimum **7a** (or **7b**), missing the point **6b**. Thus the bifurcation point *B* exists only for the MEP, but not for the gradient line (∇E does not vanish at the point *B*, and therefore only one gradient line can pass through this point).

Gradient lines can be generated or disappear only at critical points,[85,86] and therefore the behaviour of the gradient lines in the infinitesimally small surroundings of the critical point denotes a relationship between the symmetry properties of the system on the reaction path and the symmetry properties of the system at a critical point (in particular, at the minimum points and at the saddle point).[80]

In the immediate surroundings of any critical point Q_{cr} the potential energy surface $E(Q)$ can be approximately represented by the quadratic term alone of a Taylor series[82]

$$E(Q) = \frac{1}{2}\sum_{l=1}^{3N-6}\left[\frac{\partial^2 E}{(\partial Q^l)^2}\right]_{Q_{cr}} \qquad (Q^l)^2 = \frac{1}{2}\sum_{l=1}^{3N-6}\alpha_l (Q^l)^2 . \qquad (6)$$

For this type of potential the equations (5) are easily integrated, giving solutions of two types:[67,69,74,80]

trivial

$$Q^k = 0, \quad k = 1, 2, ..., 3N-6 , \qquad (7)$$

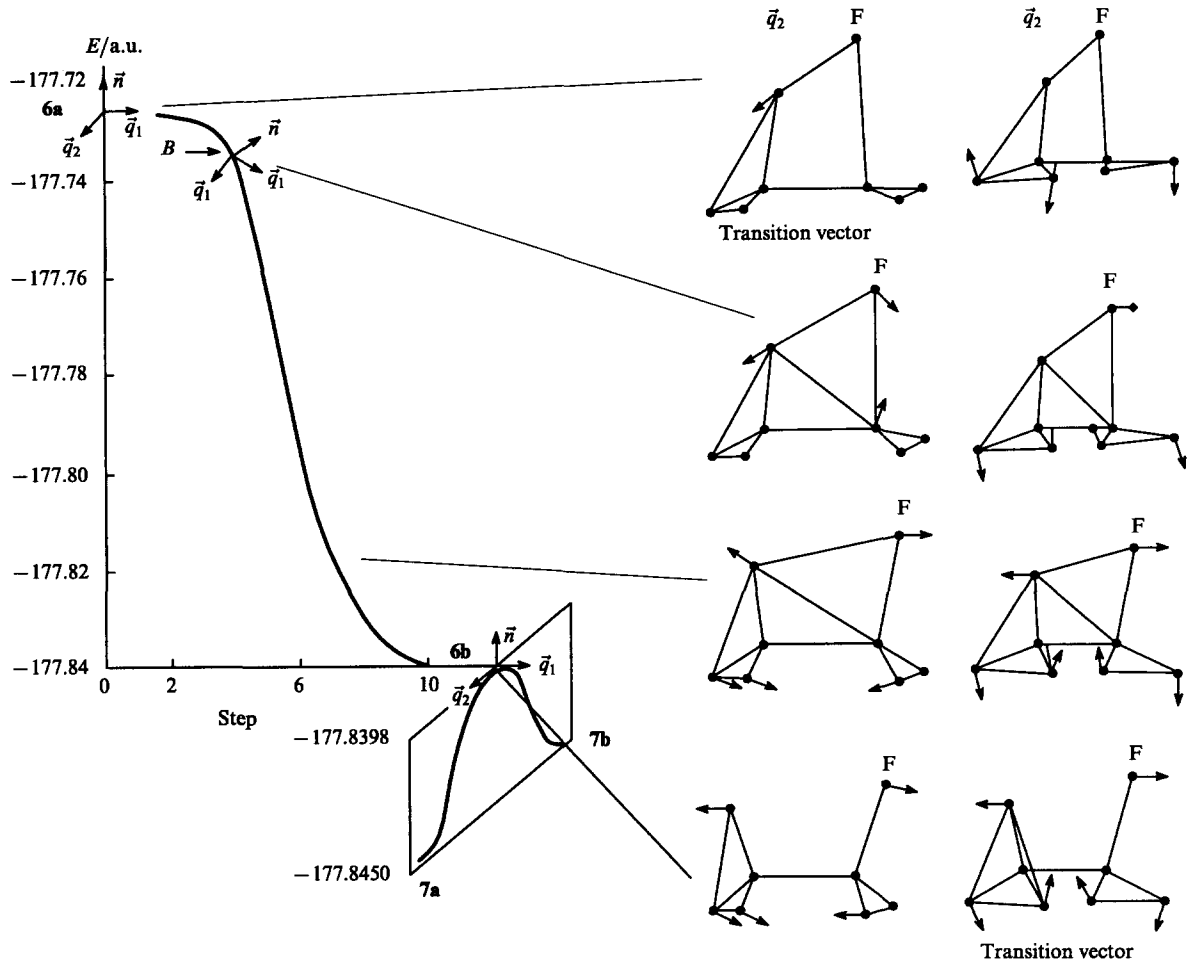


Figure 4. Evolution of the eigenvectors $\vec{q}_1$ and $\vec{q}_2$ of the Hessian along the gradient lines from the point **6a** (see Fig. 3) to the point **6b**. The vector $\vec{q}_1$ is the transition vector at the point **6a**, and the vector of the first positive eigenvalue of the Hessian at the point **6b**. The vector $\vec{q}_2$ is the vector of the first positive value of the Hessian at the point **6a** and the transition vector at the point **6b**. The forms of these vectors are shown on the right, $\vec{n}$ is the vector of the normal to the gradient line, and coincides with the direction of the E axis at the critical points.

and nontrivial

$$Q^k = (Q^k)_0 \exp(-\alpha_k t), \quad k = 1, 2, ..., 3N-6, \qquad (8)$$

where $(Q)_0$ is the initial point, corresponding to $t = 0$.

These curves are shown in Fig. 5 for the infinitesimally small surroundings of a minimum ($\lambda = 0$) and of a saddle point ($\lambda = 1$). They are asymptotic gradient lines for the total potential $E = E(Q)$ in an infinitesimally small region surrounding the nondegenerate critical points. Thus the gradient lines of any potential $E = E(Q)$ are described by the solution (7) or (8) as they approach the critical point.

For the quadratic potential (6), as for the total potential $E = E(Q)$, only one gradient line can exist in the infinitesimally small surroundings of the critical point. It passes through the given regular point Q_0 (the point X_0 in Fig. 5), and this line [a curve described by Eqn (7) or (8)] enters (or issues from) the critical point tangentially to one of the eigenvectors of the Hessian $\vec{q}_i$ ($i = 1, 2, ..., 3N-6$). In the special case of a saddle point we always find only one gradient line issuing from this point and tangential to the transitional eigenvector[79] corresponding to a negative eigenvalue of the Hessian.[67]

The eigenvectors of the Hessian $\vec{q}_i$ ($i = 1, 2, ..., 3N-6$) at the critical point are classified by irreducible representations of the symmetry point group of the molecular configuration corresponding to this critical point. It is important to note that whether or not the symmetry point group of this molecular configuration contains multidimensional representations the

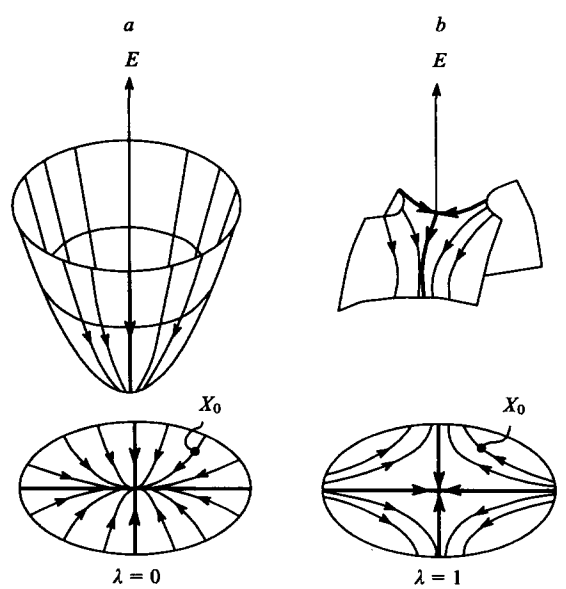


Figure 5. Principal (thick) and secondary gradient lines (thin) in the immediate vicinity of the minimum ($\lambda = 0$) and of the saddle point ($\lambda = 1$) in the entire space (*a*) and in the configurational space (*b*). X_0 are the initial points of the secondary gradient lines; the arrows on the gradient lines show the directions of decreasing potential.

gradient lines defined by the solution (8) can be tangential only to a vector belonging to a one-dimensional (nondegenerate) irreducible representation.[80]

The situations discussed above correspond to nondegenerate critical points, and in particular to minimum points and saddle points. However, there may be cases (said[4, 65] to be fairly rare) of degenerate critical points appearing on the PES, i.e. points where the condition (2) is not satisfied and one or several zero eigenvalues are found in the Hessian in addition to the six listed above. The study of the behaviour of the gradient lines in the immediate vicinity of degenerate points is one of the most important problems in the topological structure of the PES.[69, 70]

III. Symmetry of the reaction path

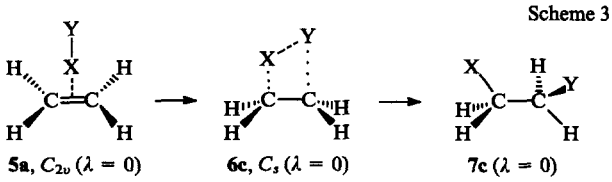
The conditions for symmetry conservation of the system along the reaction path are controlled by a theorem established by Pearson[89] in 1970, which states that the reaction path between two critical points (which are not included in the discussion) is strictly totally symmetric, i.e. that the symmetry point group of the molecular configuration is conserved over the whole length of the reaction path. It was later shown by Pechukas[67] that in practice the symmetry is conserved along the line of steepest descent (the gradient line) and that under these conditions the symmetry point group of the molecular structure of the transition state is conserved, i.e. the saddle point (upper critical point) is included in the discussion. However, Pechukas could not explain why in degenerate reactions (i.e. in reactions in which the reactant and the product are equivalent) this symmetry point group can vary at the critical points, and he was forced to treat these reactions as exceptions. Subsequently Rodger and Schipper[90, 92] also studied the conservation of symmetry along the reaction path by using the expression

$$G_q = G_R \cap G_T = G_P \cap G_T \subseteq G_R \cap G_P , \qquad (9)$$

where G_q, G_R, G_T, and G_P are respectively the symmetry point groups for the reaction, the reagent, the transition structure, and the product. Eqn (9) shows that the symmetry elements conserved along the reaction path should be symmetry elements of the reagent, of the product, and of the structure of the transition state. The expression was used[90] to formulate a hypothesis called the principle of maximum symmetry: all the symmetry relationships between reactants and products are conserved along the whole of the allowed reaction path, i.e. all the symmetry elements included in the symmetry groups of both the reactants and the products are conserved. However, examples have been reported of both degenerate and nondegenerate reactions on whose path the symmetry of the molecular configuration of the transition state can be perturbed and which do not satisfy the Pearson–Pechukas[67, 89] and the Rodger–Schipper[90] symmetry rules.

For example, as indicated by many quantum-chemical calculations in various approximations,[64, 93–102] the electrophilic addition of the XY molecule to the C=C double bond takes place according to the Scheme 3:

Scheme 3



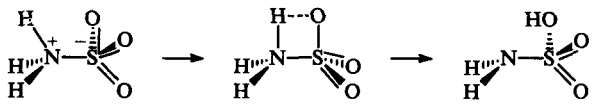
5a, C_{2v} ($\lambda = 0$) **6c**, C_s ($\lambda = 0$) **7c** ($\lambda = 0$)

where XY = HF (Refs 93–96, 98, 99), HCl (Refs 95, 96), F_2 (Ref. 97), Cl_2 (Ref. 97), HCN (Ref. 100), H_2O (Ref. 101), and MeLi, MeCu (Ref. 102).

This reaction begins with the formation of the metastable pre-reaction π-complex **5a**, followed by the transition structure **6c** with a C_s symmetry, and it ends at the minimum of the product **7c**.

It can be seen from Scheme 3 that the mirror plane of symmetry, which passes through the atoms X and Y and through the C=C bond and is retained in the initial part of the reaction (**5a** → **6c**), disappears in the final part **6c** → **7c**. But since no intermediate minima are found in the whole of the path (**5a** → **6c** → **7c**) this behaviour is inconsistent with both the Pearson[89] and Pechukas[76] theorems and the Rodger–Schipper relation.[90] A similar state of affairs has been observed[103] in the intramolecular proton transfer reaction of sulfamic acid from the zwitterion form **8** to the neutral form **10**, passing through the transition state **9** (Scheme 4):

Scheme 4



8, C_{3v} ($\lambda = 0$) **9**, C_s ($\lambda = 1$) **10**, C_1 ($\lambda = 0$)

Other examples of reactions on whose path the initial symmetry is altered through an intermediate state have been reported.[66, 104–112]

It has been shown[80] that the symmetry of a chemical system is preserved only during motions along gradient lines, and that this symmetry is determined by the symmetry of the eigenvectors of the Hessian $\vec{q}_i$ ($i = 1, 2, ..., 3N-6$) at the minimum and at the saddle point of the PES. Let us examine this problem in some detail.

The gradient lines entering an energy minimum[80] can be classified into two types: principal and secondary (see Fig. 5). The principal gradient lines define the main directions of the curvature[81, 82] at the minimum of the PES. By definition they are characterised exclusively by the eigenvectors of the Hessian $\vec{q}_i$ ($i = 1, 2, ..., 3N-6$) at the minimum, i.e. by the curvature properties of the PES in the infinitesimally small surroundings of the minimum, and they are independent of the initial conditions [the points $X_0(Q_0)$]. Evidently there are only $2(3N-6)$ principal gradient lines if allowance is made for the positive and the negative directions of each of the $\vec{q}_i$ vectors. The secondary gradient lines enter the minimum tangentially to $\vec{q}_i$ (corresponding to the lowest eigenvalue of the Hessian), and form an infinite series of gradient lines defined by the initial points $X_0(Q_0)$.

The symmetry point group of the molecular configuration at some point X on the gradient line defines the symmetry point group of the tangential vector $\nabla E(X)/|\nabla E|$, and this symmetry group (according to Pearson's theorem) is conserved over the entire length of the gradient line. Thus the symmetry of the gradient line, defined as the symmetry group of the vector $\nabla E/|\nabla E|$, is uniquely determined by this vector.

The direction of the principal gradient line in the configurational space coincides with that of one of the vectors $\vec{q}_i$ ($i = 1, 2, ..., 3N-6$) in the infinitesimally small surroundings of the minimum point. This means that the tangential vector $\nabla E(X)/|\nabla E|$ at the point X ($X \neq X_{min}$), which belongs to immediate surroundings of the minimum, has the symmetry of the corresponding vector $\vec{q}_i$. The symmetry point subgroup of the vector $\vec{q}_i$ is defined as the plurality of symmetry elements of this vector.

Thus the symmetry of the principal gradient line is given by the symmetry group of the Hessian vector $\vec{q}_i$, to which it is tangential at the minimum point. A similar analysis of the symmetry of a gradient line emerging from the saddle point tangentially to a transition vector shows that its symmetry group is determined by that of the transition vector. If the gradient line emerging from the saddle point enters the minimum along a principal direction the symmetry group of the transition vector coincides with that of the corresponding vector $\vec{q}_i$.

The direction of the secondary gradient lines in the configurational space does not coincide with the direction of the vector $\vec{q}_1$ in the infinitesimally small surroundings of the minimum

point. Therefore arguments similar to those used above for the principal gradient lines are not applicable to secondary lines. For the secondary gradient lines we may only conclude that the symmetry group cannot be higher than the symmetry group of the vector $\vec{q}_1$ to which they are tangential.

The rules for the conservation of symmetry along the reaction path can be formulated as follows.

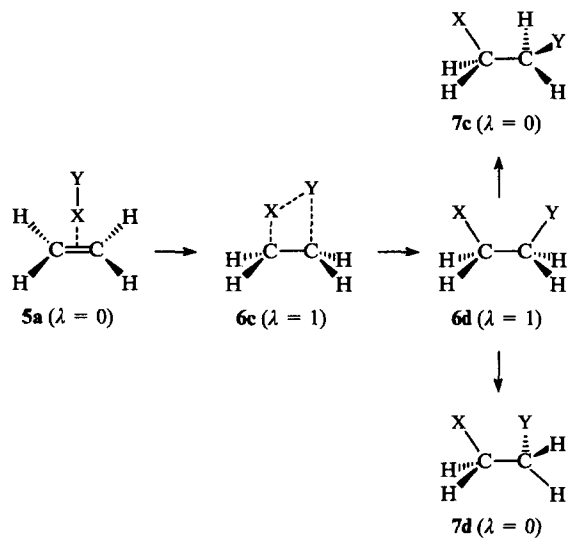
(1) The symmetry point group of the structure vector of the transition state is conserved along a gradient line. This symmetry group can either coincide with the symmetry group of the corresponding eigenvector of the Hessian for the minimum (if the gradient line enters the minimum along a principal direction) or it can have a lower value (if the gradient line enters the minimum along a secondary direction).[80]

(2) A change in the symmetry point group of the molecular configuration of the system is possible only at the critical points.[67, 113, 114]

(3) The symmetry point group of the transition vector, which is conserved along the gradient line, should also be a subgroup of the symmetry point groups of the reactant, of the transition state structure and that of the product, or of all three critical points connected by the given gradient line.[113]

The first rule states that the symmetry is conserved along the gradient line, and not along the MEP, and therefore we must first of all identify all the gradient lines which contribute to the reaction path of the given reaction by analysing the conservation of symmetry along each gradient line.

Scheme 5



Thus, if the reaction path consists of two gradient lines[7] (see Scheme 5, and also Scheme 3 and Fig. 3), the appropriate symmetry is retained along each of these lines. In the initial stage **5a** → **6c** → **6d** the reaction path is defined by the gradient line along which the mirror plane of symmetry passing through the atoms X and Y and through the two carbon atoms is conserved (C_s symmetry). In the final stage **7c** → **6d** → **7d** the reaction path is defined by the other gradient line (corresponding to internal rotation round the C–C bond, along which the symmetry conservation conditions are different from those which apply to the first gradient line.

The PES of sulfur tetrafluoride SF_4 has a more complex structure (Fig. 6). For this system the path of the enantiomerisation reaction consists of three nonequivalent gradient lines. The gradient line passing through the saddle point (corresponding to the planar transition structure with D_{4h} symmetry) connects three neighbouring saddle points (transition structures corresponding to two pyramidal structures with C_{4v} symmetry and one planar structure with D_{4h} symmetry).

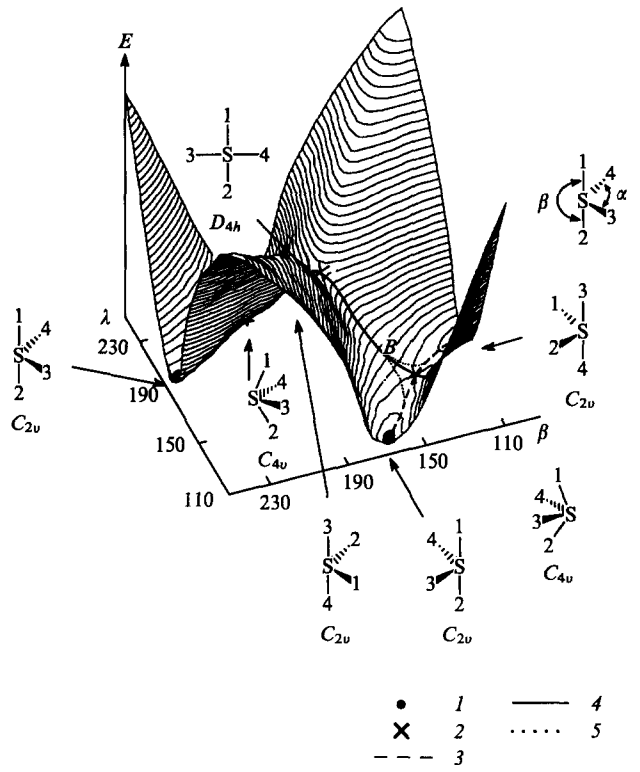
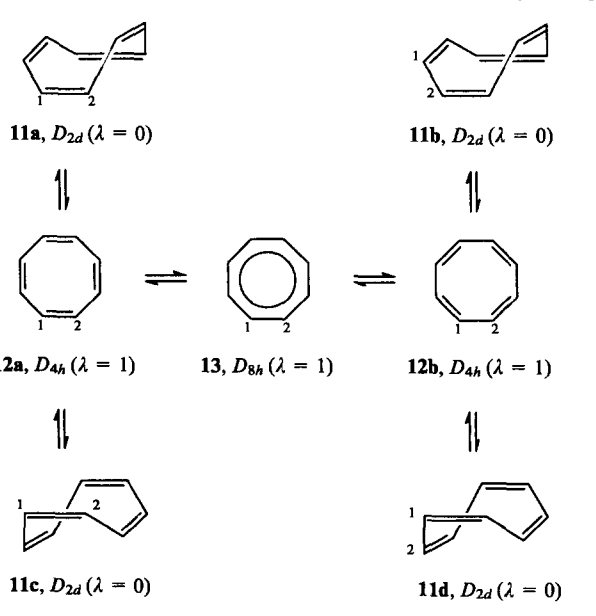


Figure 6. Potential energy surface of the enantiomerisation reaction of the sulfur tetrafluoride molecule in α, β coordinates according to ab initio calculations (STO 6-31G*).[108] The angles α and β are defined on the right of the figure.[108] (*1*) Minima; (*2*) saddle points (transition states); (*3*) Berry pseudorotation; (*4*) inversion of the C_{4v} structure of SF_4; *B* is the bifurcation point where the minimum energy path (*5*) breaks into two and diverges from the gradient line.

We should note that at the point *B* the minimum energy path is split into two and diverges from the gradient line. The other two gradient lines correspond to Berry's pseudorotation reaction[115] in sulfur tetrafluoride. A similar structure is observed in the PES for the 1,3 proton shift reaction in the zwitterion **8** (see Ref. 103) and in other reactions.[104, 105]

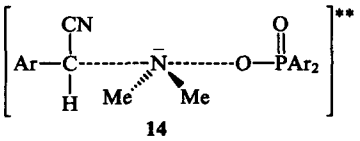
Scheme 6



The isomerisation of the cyclooctatetraene (COT) molecule,[116-121] first synthesised[118] by Willstätter in 1913, is a remarkable example of a reaction whose path consists of several non-equivalent gradient lines (Scheme 6). An unusual stereochemical lability (the fast valence isomerisation **11a** ⇄ **11b**, taking place through the planar structure **13** with an activation barrier of 14 kcal mol^{-1}) was detected by NMR more than 30 years ago.[112] Later studies[123,124] by dynamic NMR detected a lower-energy conformational transition in this system: the ring inversion **11a** ⇄ **11c**, with a barrier of ~10 kcal mol^{-1}. The transition structures in this process could be either the planar structure **12** (D_{4h}) or various nonplanar structures. The planar configuration **13** (D_{8h}) is a classical example of an antiaromatic system.[64,119] If the structure **12** corresponds to the transition state the difference in energy between the structures **12** and **13** will be the energy of the antiaromatic destabilisation (delocalisation) in the molecule. Therefore establishing the nature of the stationary points on the PES of cyclooctatetraene corresponding to the structures **12** (D_{4h}) and **13** (D_{8h}) has stimulated the interest of theoretical chemists for many years.[106,125-127] It was established relatively recently[106] by accurate ab initio calculations (CAS SCF/3-21G* and 6-31G*+ΔZPE) with full allowance for the force constants that these two planar structures are transition states ($\lambda = 1$) for the ring inversion and the valence isomerisation reaction respectively. In this case the structure of the PES is similar to that shown in Fig. 6. Surprisingly, however, though the vector of the transition state **13** shows unambiguously that the reaction path (gradient line) issuing from the PES point corresponding to **13** (D_{8h}) should arrive at the point **12** (D_{4h}), the authors[106] assume that the reaction path of the valence isomerisation misses this structure by branching on the slope of the PES.

The nucleophilic substitution (S_N2) at the nitrogen atom[128-133] is an interesting example of a reaction with a complex path. By using two isotopic labels it was shown experimentally[133] that the nucleophilic substitution reaction on the nitrogen atom of *N*,*N*-dimethyl-*O*-(diarylphosphinyl) derivatives passes through the structure of a transition state of the type **14**, which is similar to the transition structure of the S_N2 reaction at a carbon atom. This confirms the generality of the Walden inversion in tetrahedral or pseudotetrahedral configurations (in which the unshared pair of the central atom plays the role of a phantom ligand) in nucleophilic substitution reactions (Scheme 7).

Scheme 7



14

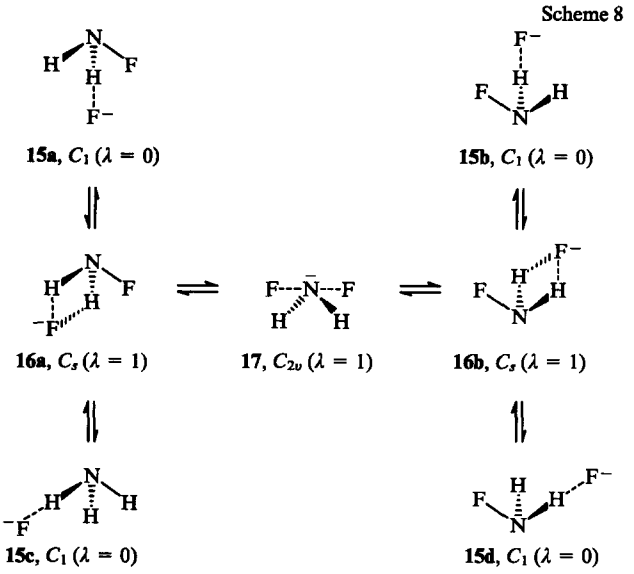
Ab initio calculations[107] (SCF TZP+/CISD) carried out with adequate precision within a year of the previous work[133] on the model reaction (Scheme 7)

$$F^- + H_2NF \rightleftarrows FNH_2 + F^-,$$

confirmed the original conclusions[133] and showed that the reaction begins with the formation of the nondipolar complex **15** having a linear F$^-\cdots$H–N bond and passes through the transition state **17** with a C_{2v} symmetry and an activation barrier of 24 kcal mol^{-1} (Scheme 8). This barrier is higher than the corresponding activation barrier for the S_N2 reaction on the carbon atom, calculated (by SCF DZDP/CISD methods) to be 17.1 kcal mol^{-1} (see Ref. 134). According to the proposed mechanism the fluoride ion can be transcoordinated between two NH bonds through the transition state **16** (C_s) by surmounting an activation barrier of 4.6 kcal mol^{-1}.

Thus, according to published calculations,[107,135] the general reaction path outlined in Scheme 6 is very similar to that of the sulfur tetrafluoride enantiomerisation and the cyclooctatetraene valence isomerisation reactions, and can be represented by the

Scheme 8



PES shown in Fig. 7. The gradient line issuing from the saddle point **17** transition state with C_{2v} symmetry) enters the neighbouring saddle point **16a** (or **16b**, transition state with C_s symmetry) corresponding to the peak of the activation barrier for the transcoordination of the fluoride ion from one NH bond to the next. At the point on the PES corresponding to the state **16a** the system passes from one gradient line to the next, and reaches the minima **15a** and **15c** (or **15b** and **15d**) along both branches of the line.

The conclusion that two (or more) saddle points cannot exist on the same gradient line follows from the Fernandez–Sinanoglu theorem.[136] It also follows that the reaction path must split into two before the second saddle point (the second transition state). The proof of the Fernandez–Sinanoglu theorem is based on the hypothesis that the reaction path always consists of a single gradient line connecting the saddle point with a minimum. However, there are no logical or physical reasons for this condition to be satisfied in general. As can be seen from the examples discussed above, the reaction path may consist of several gradient lines which the system follows sequentially. This means that the Fernandez–Sinanoglu theorem does not apply in general, and that there are no limitations (other than the Morse expressions,[137] which establish strict relationships between the numbers of nondegenerate critical points of different order in a defined region of the PES) on the character of the critical points lying on one gradient line (see also Refs 25 and 66).

According to the first rule of symmetry conservation along the reaction path (see above), the symmetry point group conserved along a gradient line is not that of the molecular configuration of the transition structure as had been suggested,[64,67,75,90-92,113,114] but that of the transition vector. This important difference from previously formulated rules[67,90] removes existing discrepancies in our understanding of the conservation of symmetry along the reaction path, including the exceptions from the Pechukas rules.[67] We shall illustrate this conclusion with two examples: the inversion in the ammonia molecule and the internal rotation in ethane. As can be seen from Fig. 8, the symmetry point groups of the vector of the rotational mode at the minimum and of the transitional vector at the saddle point coincide in the ethane molecule, and are equal to D_3. Similarly, in the ammonia molecule the symmetry point group C_{3v} is conserved. These symmetry groups do not change during the transition from the minimum of the reactants through the transition state to the minimum of the products. However, the corresponding point groups of the molecular configurations change from D_{3d} to D_{3h} and back to D_{3d} for ethane, and for ammonia they change in the sequence C_{3v}–D_{3h}–C_{3v}.

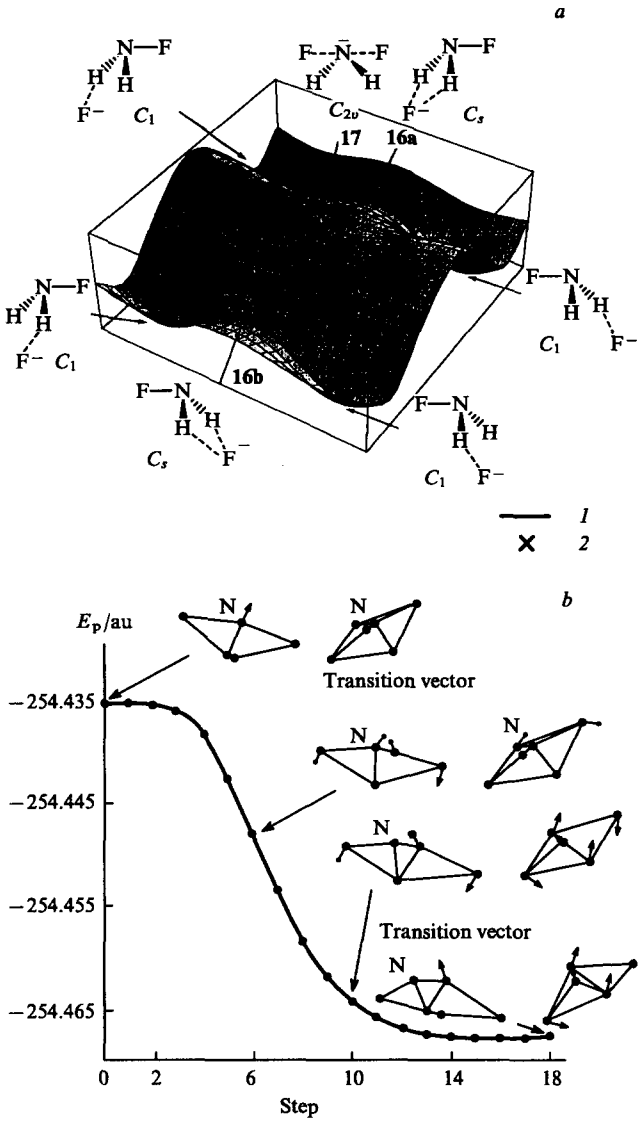


Figure 7. Potential energy surface (*a*) of the nucleophilic substitution reaction $F^- + H_2NF \rightleftarrows FNH_2 + F^-$ and evolution (*b*) of two eigenvectors of the Hessian along the gradient line (*1*) from the saddle point **17** to the neighbouring saddle point **16a** according to SCF/DZP ab initio calculations;[135] (*2*) are the saddle points.

Rule (2) [like rule (3)] is a corollary of rule (1). Unless used in conjunction with rule (1) it confuses our understanding of the principle of symmetry conservation along the reaction path.

We shall interpret the symmetry of a point on the PES (including a critical point) as the symmetry point group of the corresponding molecular configuration. The symmetry subgroup of each vector $\vec{q}_i$ is unambiguously determined by the symmetry point group of the molecular configuration at the critical point. Obviously, the inverse statement is equally valid: the symmetry subgroups of all the $\vec{q}_i$ vectors uniquely define the total symmetry group of the molecular configuration. In this case we may conclude that the symmetry of any critical point is determined by the symmetry of all the gradient lines entering or emerging from that point.[80] In other words each gradient line contributes to the given critical point its own symmetry subgroup, and the symmetry point group of the molecular configuration in the same critical point is determined by the combined symmetries of all three gradient lines. Therefore when the molecular system has reached a critical point (including a minimum) the order of its symmetry group can only rise.[114]

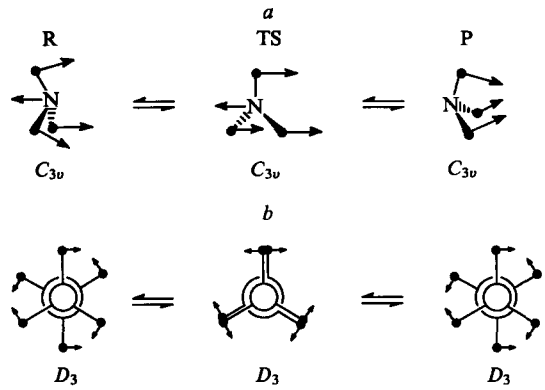


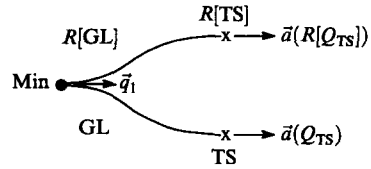
Figure 8. Reactions producing inversion of the pyramidal configuration of bonds in the ammonia molecule (*a*) and internal rotation around the C–C bond in ethane (*b*). The arrows show the components of the normal and of the transition vectors at the minima. R are the reactants, P are the products, TS is the saddle point.

IV. Reaction paths consisting of several equivalent gradient lines

1. Reaction paths consisting of two equivalent secondary gradient lines

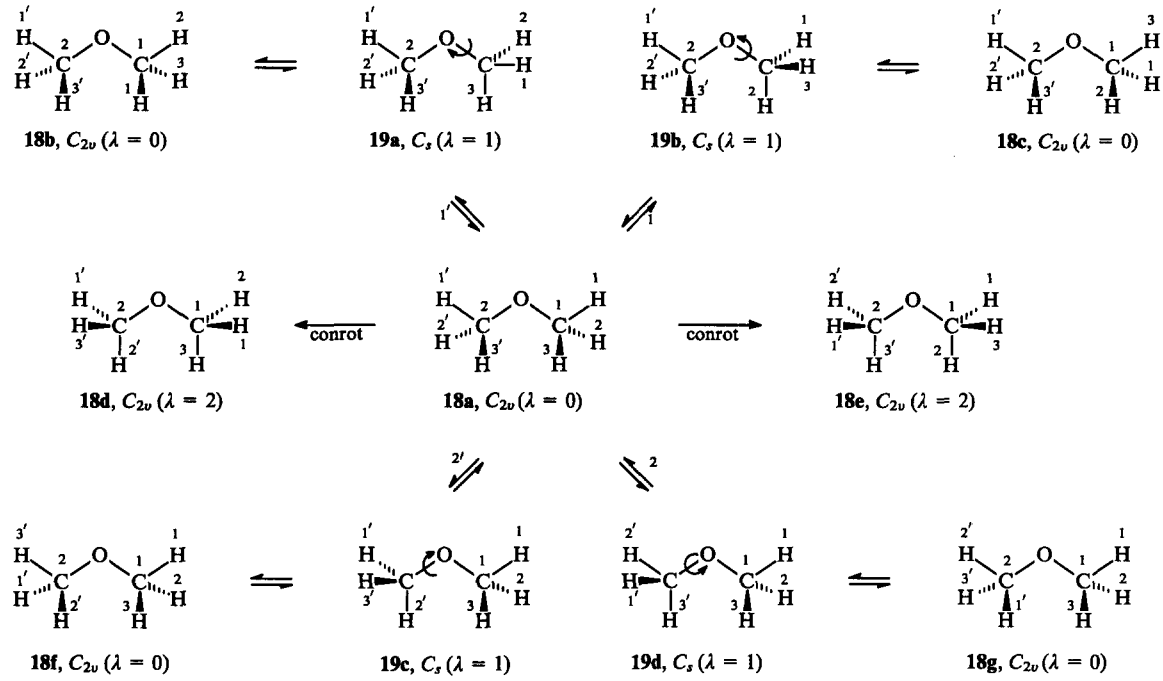
Unlike the symmetry group of principal gradient lines (see above) the symmetry group of a secondary gradient line entering a minimum can either coincide with the symmetry group of the Hessian vector $\vec{q}_1$ (corresponding to the lowest eigenvalue) or be its subgroup.[80] Therefore, if a secondary gradient line connects the minimum with any transition state the symmetry group of the transition state [according to the rule (1), see above] can either coincide with the symmetry group of the vector $\vec{q}_1$ at the minimum point or be its subgroup. We shall assume that $\vec{q}_1$ has at least one nontrivial symmetry element R, and that the transition state TS with the transition vector $\vec{a}(Q_{TS})$ is found on one of its secondary gradient lines. In this case the symmetry conditions require that in addition to the transition state TS an equivalent state R[TS] with a transition vector $\vec{a}(R[Q_{TS}])$ must exist. Then the minimum point is coupled with the two equivalent transition states TS and R[TS] by the two symmetry-equivalent secondary gradient lines GL and R[GL], as illustrated in Scheme 9.

Scheme 9



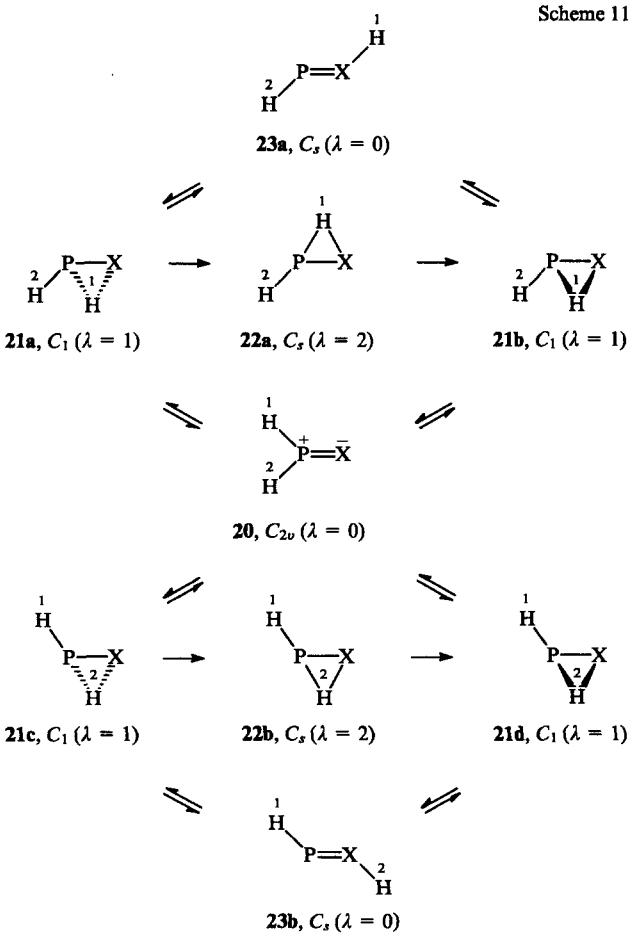
In this case the gradient path of the chemical reaction consists of two equivalent (physically indistinguishable) gradient lines. Various combinations are possible: each of the equivalent gradient lines leads to a different minimum (Figs 9*a* and 9*b*, see over), the lines lead in pairs to the same minimum (Figs 9*c* and 9*d*), etc. Examples of reactions whose equivalent paths lead to the same minimum[14,23,130,139] or to different minima[14–21,139–141] have been reported. If the molecule contains two stereochemically equivalent nonrigid groups which can independently undergo a conformational rearrangement (for example, rotation around single bonds, Scheme 9) we may observe a gradient reaction path consisting of two equivalent gradient lines. For example, in propane,[15] dimethyl ether,[16,17] and other molecules[18,19,138–141] two methyl groups can rotate independently of each other. Under these conditions each line in the gradient reaction path leads to a different minimum (see Fig. 9*b*). In particular, for the dimethyl ether molecule[16] this type of gradient reaction path can be illustrated by Scheme 10 (see over).

Scheme 10



Each of the methyl groups in this molecule can rotate independently. Four equivalent gradient lines, each passing through its own transition structure **19a–19d** and leading to a separate minimum **19b–19g**, emerge from the minimum **18a**. The routes 1 and 2 form one gradient reaction path, the routes 1′ and 2′ form another.

Scheme 11



An example of a reaction corresponding to the case shown in Fig. 8*c* is the 1–2 shift of the hydrogen atom in the $H_2P{=}N$ and $H_2P{=}P$ molecules (Scheme 11). Ab initio calculations[23] allowing for the correlation energy of the electrons in the $H_2P{=}N$ and $H_2P{=}P$ molecules show that in the migration process **20** ⇄ **23** the hydrogen atom moves out of the (initially) planar molecule. The out-of-plane (inversion) mode of the normal vibration of the structure **20** corresponds to the lowest frequency. In these reactions the transition states are the states **21a–21d**. The states **22a** and **22b** corresponds to a critical point with $\lambda = 2$ (see Refs 23 and 142). The potential energy surface of the system is shown in Fig. 10. The two secondary gradient lines emerging from the minimum **20** tangentially to the vectors $+\vec{q}_1$ and $-\vec{q}_1$ (out-of-plane inversion mode), which pass through the two saddle points **21a** and **21b** and terminate in the same neighbouring minimum **23a**, form two equivalent gradient reaction paths.

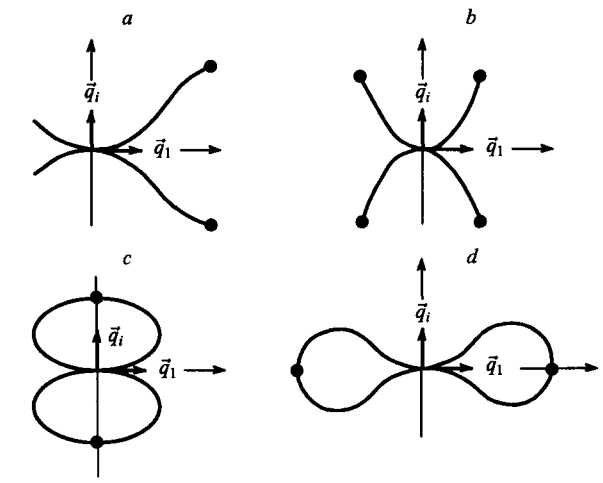


Figure 9. Variants of the two-line reaction paths. (*a*) Two branches of two equivalent secondary gradient lines enter two minima; (*b*) each of the branches of two gradient lines enters its own minimum; (*c*) two branches of one gradient line enter the same neighbouring minimum; (*d*) the branches of two different gradient lines enter the same neighbouring minimum.

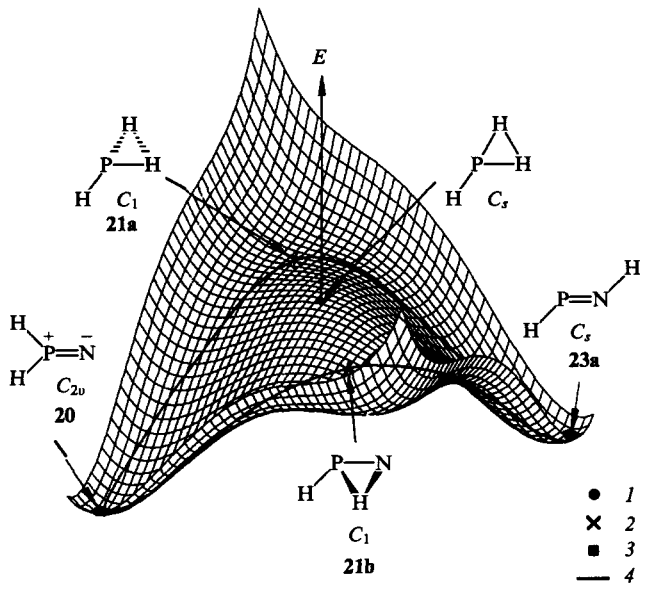
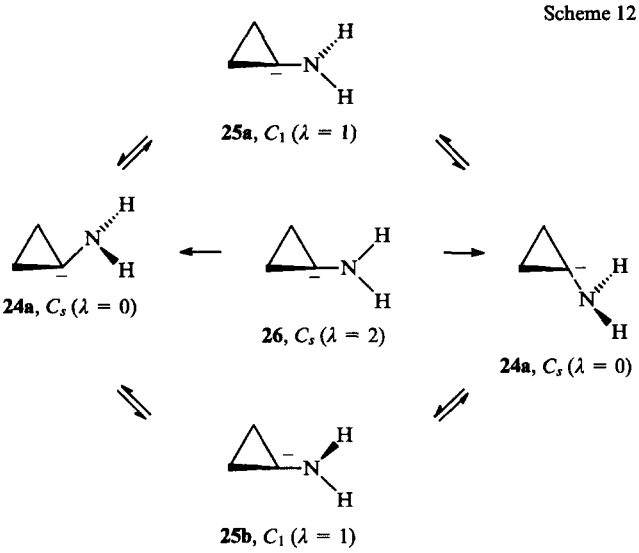


Figure 10. Potential energy surface of the 1,2 hydrogen atom shift in the H_2PN molecule (**20**) according to ab initio calculations.[23] (*1*) minima; (*2*) saddle points (transition states); (*3*) critical points with $\lambda = 2$; (*4*) gradient reaction path consisting of the two gradient lines **20** ⇄ **21a** ⇄ **23a** and **20** ⇄ **21b** ⇄ **23a**.

The principal gradient line issuing tangentially to $\vec{q}_2$ (the mode corresponding to the 1,2-H shift) passes through the critical point with $\lambda = 2$ (structure **22a**) and enters the minimum **23a**. This topology of the PES is consistent with the correlation of the atomic shift vectors along the whole length of the gradient line between two minima.[142]

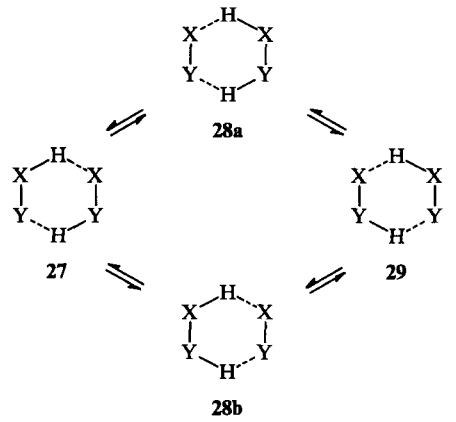
Scheme 12



The inversion reaction at the carbanion centre of the aminocyclopropyl anion **24** (Scheme 12) is an interesting example. Ab initio calculations [MP2/6-31 + G(d)//6-31 + G(d)][138] predict that the inversion reaction passes through two enantiomeric asymmetric (C_1) transition states **25a** and **25b** with an activation barrier of 30.1 kcal mol^{-1}. This means that the gradient path of the reaction is described by two equivalent gradient lines. The state **26** (C_s or C_{2v}), which unfortunately was not studied by Chou et al.,[138] should correspond to a critical point with $\lambda = 2$ on the PES of the carbanion.

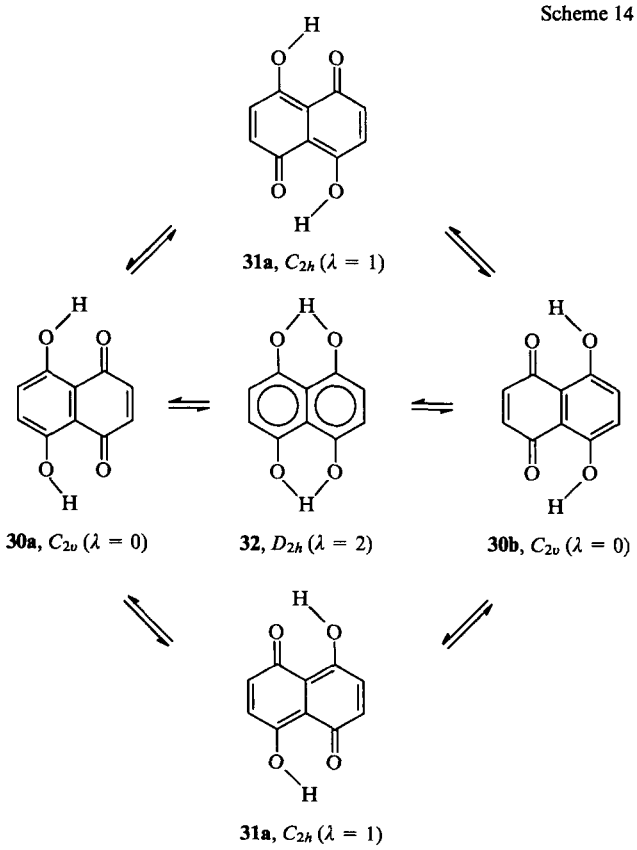
An important class of reactions described by two equivalent lines includes the double proton transfer reactions in various organic compounds,[143-167] such as porphyrin,[143-147] tetraphenylchlorin,[149] oxalamidine,[150,151] azophenone,[150-155] naphthazarin,[156-161] and the dimer of formamidine.[162-164] In all these systems the transfer of two protons occurs[149] by the general Scheme 13.

Scheme 13



The states **28a** and **28b** on the PES can be transition states (concerted process) or they can correspond to intermediate minima (multistage process). Nevertheless in both cases the chemical reaction **27** ⇄ **29** is described by two equivalent routes, **27** ⇄ **28a** ⇄ **29** and **27** ⇄ **28b** ⇄ **29**, along which the chemical system can decompose with equal probabilities. Thus, the double proton transfer in the naphthazarin molecule **30a** ⇄ **30b** (Scheme 14) passes through the transition state **31** with an activation barrier of 25 kcal mol^{-1}, calculated by an ab initio method in an STO-3G basis.[156] As was shown by the calculation[156] the symmetrical structure **32** (D_{2h}) corresponds

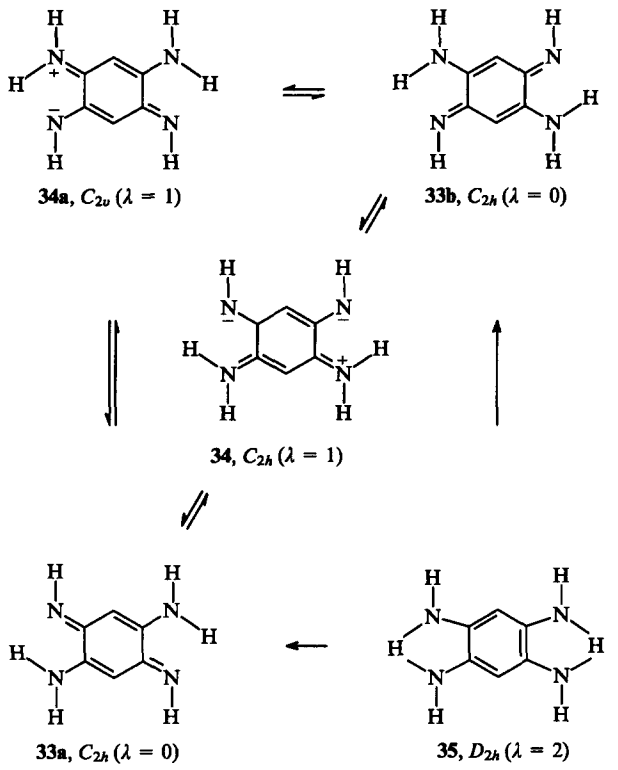
Scheme 14



to a critical point with $\lambda = 2$. These results agree with NMR data[158,159] and with IR spectroscopy results.[161] However, the small energy difference (3 kcal mol^{-1}) observed[156] between the structures **32** and **31**, which may be strongly affected by allowing for the correlation energy,[14] calls for a more careful examination of these results.

The next example of a reaction which has been studied in reasonable depth is the double proton transfer in the azophenine molecule **33** (Scheme 15).[150–155] The automerisation of this molecule was explained (from measurements[150] of the kinetic and isotopic effects in derivatives of azophenine) by the simultaneous synchronous (concerted) transfer of two protons through the transition state **35** with an activation barrier of 10 kcal mol^{-1}.

Scheme 15



However, later calculations by AMI[153] and by ab initio methods[155] (MP2/3-21G//3-21G) showed that the reaction **33a** ⇄ **33b** takes place in stages through the zwitterion intermediate structure **34** ($\lambda = 0$) with an activation barrier of 17.3 kcal mol^{-1}, which exceeds the experimental value by 7.3 kcal mol^{-1}. Under these conditions the structure **35** (D_{2h}), as in the case of naphthazarin, corresponds according to the calculations[153,155] to a critical point with $\lambda = 2$. The observed discrepancy between experimental and theoretical data stimulated a careful re-examination of the experimental measurements.[152] New experiments[152] carried out immediately after the theoretical calculations[155] confirmed the conclusion[153,155] that the reaction **33a** ⇄ **33b** takes place in stages through the zwitterion intermediate structure **34**. However, the difference between the theoretical height[155] of the activation barrier (17.3 kcal mol^{-1}) and the experimental value[150] (~10 kcal mol^{-1}) is attributed to the choice of an insufficiently broad basis[155] and to the failure to allow for the effect of substituents on the barrier height.

Thus the path of the reactions discussed above (Schemes 9–15) and of some other reactions consists essentially of two equivalent gradient lines along which the chemical system can move with equal probabilities.

The existence of these reaction paths was first predicted by Salem,[168] who used the term narcissistic to describe them.

2. Reaction paths consisting of three or more equivalent gradient lines

A chemical reaction gradient path consisting of three or more equivalent gradient lines can be realised for chemical systems having a point group symmetry containing a triad (or higher) symmetry axis.[80] In this case the gradient lines approach the minimum in a radial direction in the space generated by the $\vec{q}_k$ vectors from a multidimensional representation. Two situations may be realised in this way: in the first each equivalent gradient line leads to its own minimum, and in the second all the equivalent gradient lines enter the same neighbouring minimum. Good examples of the first case are the isomerisation (topomerisation) of bulvalene,[9] mentioned in the Introduction, and the opening of the three-membered ring of the ozone molecule.[22]

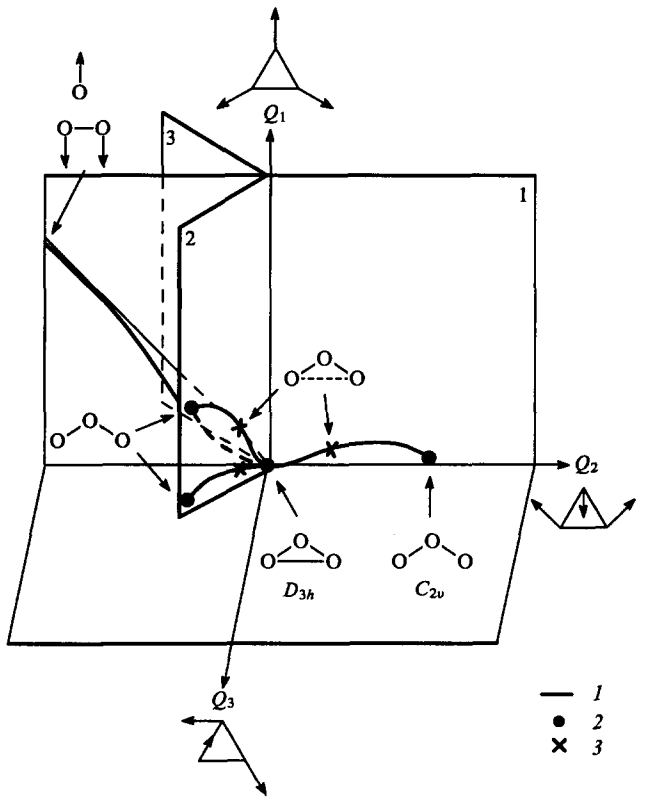
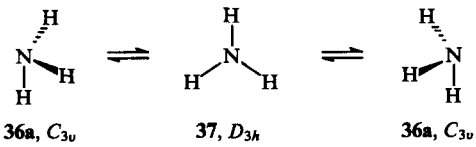


Figure 11. Equivalent gradient lines (*1*) leading to three equivalent transition states in the ring opening reaction of the D_{3h} form of the ozone molecule. The normal Q_i coordinates (i = 1, 2, 3) of the cyclic D_{3h} form are used as coordinates.[22] (*2*) Is a minimum; (*3*) is the transition state. The components of the normal $\vec{q}_i$ vectors (i = 1, 2, 3) are shown on the side of the coordinate axes.

Let us consider in more detail the opening of the three-membered ring (D_{3h}) of the ozone molecule. The gradient path of this reaction consists of three equivalent gradient lines connecting the central minimum (D_{3h}) with three equivalent minima (C_{2v}) corresponding to the open form of ozone (Fig. 11). In this case the global coordinates were taken to be the normal coordinates of the D_{3h} form. Unlike the local coordinates, which give an adequate description of the system only in a small region of the configurational space, the global coordinates fully describe the configurational space of the molecular system over the whole range of internal coordinates. The figure also shows how the gradient line corresponding to a motion opposite to that of the ring-opening reaction leads to the removal of an oxygen atom from the ozone molecule. Along this line the normal mode is converted into the local mode.[169,170] The theory of local modes was developed to explain the breaking of individual chemical bonds, for which the theory of normal modes could not account.

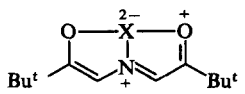
An example of a reaction in which all three gradient lines connect two neighbouring minima is provided by the inversion of the pyramidal bond configuration in the trifluorophosphine molecule.[24,25] The history of the discovery of this uncommon reaction path is instructive and we shall briefly dwell on it. We know[14,171-175] that the inversion of the ammonia molecule **33a** ⇄ **33b** takes place through a planar (D_{3h}) transition state **37** (Scheme 16).

Scheme 16



36a, C_{3v} **37**, D_{3h} **36a**, C_{3v}

It has long been assumed that a planar (D_{3h}) structure of the type **37** is the only possible transition state for the inversion of various three-coordinated pyramidal (C_{3v}) structure. This hypothesis is confirmed by the many published studies of inversion processes in different systems, and no exceptions to it have so far been reported.[13,14,171-175] However, the synthesis[176-178] of the compound **38**, containing a planar T-shaped bond configuration on the pnictogen atoms (P, As, Sb, and Bi) suggested that the T configuration may act as the transition state in the inversion of the XF_3 molecule (where X = P, As, Sb, Bi):



38

X = P, As, Sb.

In this way it was shown by ab initio calculations[179,180] that in the pyramidal molecules[179] PF_3 and SbF_3^+, and AsF_3 and SbF_3 (see Ref. 100) having a C_{3v} symmetry, the inversion takes place through the T-shaped C_{2v} form rather than through the planar (D_{3v}) form. This difference in the structure of the transition state between PF_3 and the ammonia molecule is unexpected. It can be attributed to the fact that the electrostatic repulsion between the unshared pair and the ligands is much smaller in the T-shaped form of the PF_3 molecule than in the D_{3h} form, whereas in the ammonia molecule (and in the other systems which invert through a planar D_{3h} state) the opposite is true.[179]

The appearance of a T-form as the transition state on the inversion path of the XF_3 molecule (X = P, S^+, As, Sb) requires the inversion mechanism to be reconciled with the microscopic reversibility principle,[181] according to which the path of the inversion reaction should contain three equivalent (topomeric) T-shaped transition structures[24] through which pass three equivalent gradient lines which form the gradient path of the reaction.

In the region between the two stable pyramidal C_{3v} forms the potential energy surface of PF_3 has a D_{3h} symmetry. The potential energy surface can be represented as a diagram of the gradient lines which connect the critical points (Fig. 12).[24]

The two axial corners of this bipyramid correspond to the two stable pyramidal structures **39a** and **39b** (C_{3v}), the three equatorial corners to the three T-shaped transition states **40a** – **40c** (C_{2v}). The centre of the bipyramid corresponds to the planar structure **41** (D_{3h}). All the lines in this figure are gradient lines issuing from a critical point with $\lambda \geq 1$ (structures **40**–**42**) in the direction of one of the imaginary frequency vectors. The gradient lines emerging from the transition structures **39a**–**39c** form (as a combined path) the gradient paths of the inversion reaction. In Fig. 12 they are shown as the edges of the pyramid. The axial line passing through the two axial corners and the centre of the bipyramid corresponds to the usual inversion (as in the ammonia molecule).

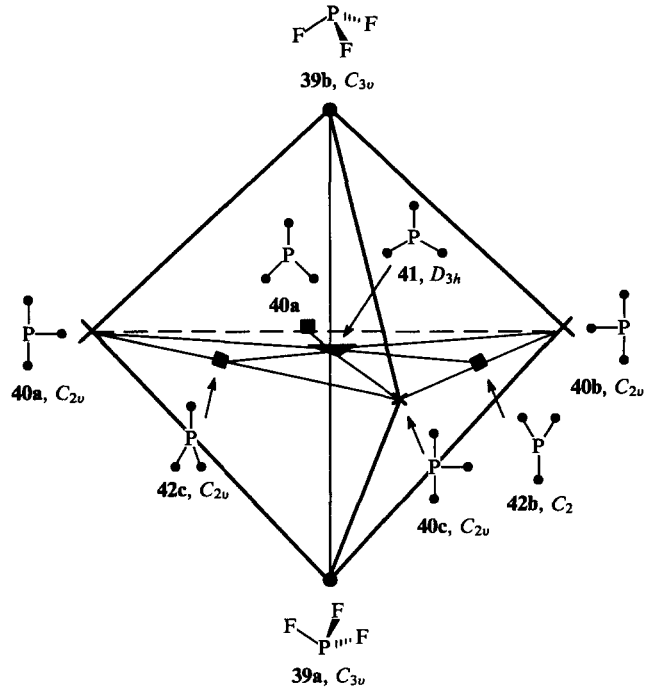
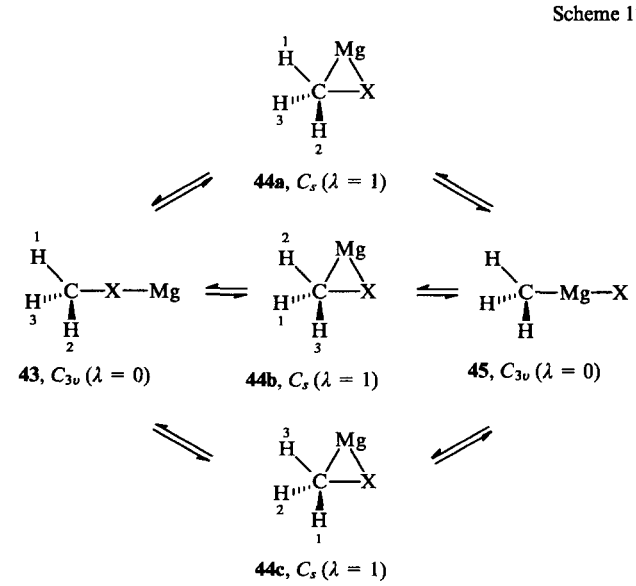


Figure 12. Diagram of the inversion reaction in the PF_3 molecule.[24] The thick lines denote three equivalent gradient lines passing through three equivalent transition states **40a**–**40c** (shown by crosses). The rectangles and the triangle show respectively the critical points of the second ($\lambda = 2$) and of the third order ($\lambda = 3$).

The lines joining the centre of the bipyramid with its equatorial corners correspond to three gradient lines on which the structure **41** (D_{3h}) becomes distorted into **40** (C_{2v}). All the transition structures are connected by a gradient line corresponding to the 'internal pseudorotation' of the T-shaped structure, simulating the true pseudorotation in ClF_3 (see Ref. 182) and other AX_3 systems (see Ref. 183).

Another interesting example of a reaction whose path consists of three equivalent gradient lines connecting two neighbouring minima is provided by the insertion of a magnesium atom into the C–X bond (X = F, Cl) of the halogenomethanes H_3C-X with formation of a Grignard reagent (Scheme 17). This reaction begins[184] with the formation of the complex **43**, after which

Scheme 17



44a, C_s ($\lambda = 1$)

43, C_{3v} ($\lambda = 0$) **44b**, C_s ($\lambda = 1$) **45**, C_{3v} ($\lambda = 0$)

44c, C_s ($\lambda = 1$)

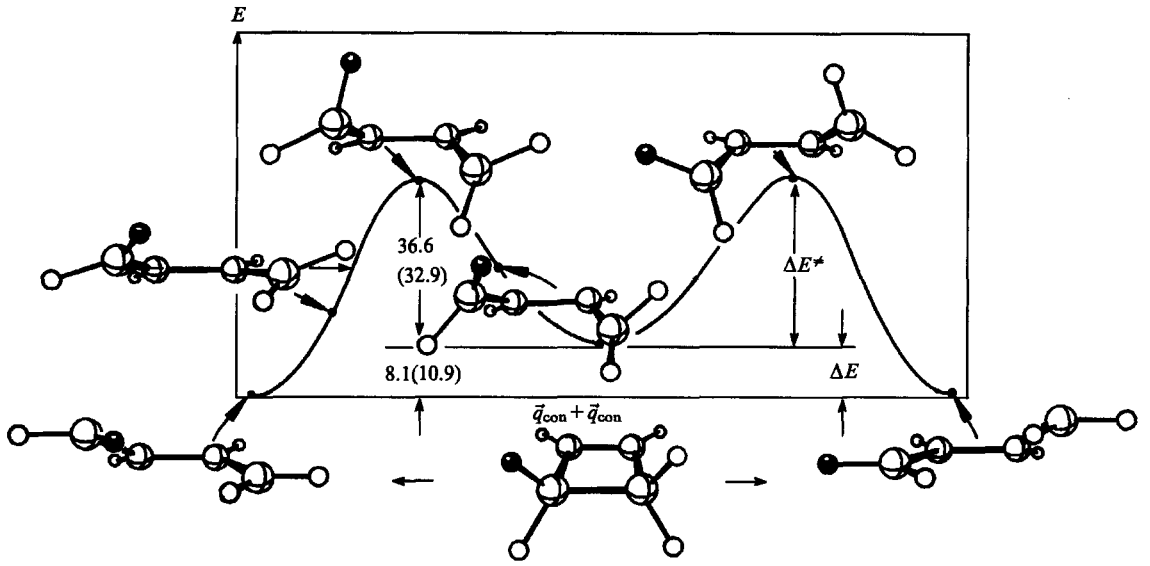


Figure 13. Mechanism of the pericyclic transformation reaction of the cyclobutene molecule into the gauche structure of 1,3-butadiene along the allowed conrotational path. The Figure shows the geometrical transformation of the water molecule along both directions of motion $+\vec{q}_{con}$ and $-\vec{q}_{con}$. Experimental [199-201] and calculated [188,193] values of the activation barrier and of the heat of reaction are given (numbers in parentheses and without parentheses respectively, kcal mol^{-1}).

[according to MP4 SDTQ/6-311G(dp) ab initio calculations [184]] the gradient path of the reaction passes simultaneously in three directions through the three equivalent transition states **44a–44c** and terminates at the minimum **45**. The activation barriers calculated for the reaction of (25) with X = F and Cl are 31.2 and 39.4 kcal mol^{-1} respectively.

V. Unimolecular reaction mechanisms

The term mechanism of a chemical reaction is usually applied to the totality of the elementary steps which contribute to the conversion of the reactants into the products.[185,186] For the purpose of this discussion it is more convenient to use the concept of the mechanism of an elementary reaction step,[187] which denotes the totality of the electronic–nuclear transformations of the molecular system on the reaction path from the given minimum to the neighbouring minimum. In Fig. 13 we show the mechanism of the pericyclic ring opening reaction of the cyclobutene molecule, including the geometric transformation of the system along the reaction path, established by various methods.[188-202] During the reaction the system moves along two equivalent gradient lines, which emerge from the minimum tangentially to the vectors $+\vec{q}_{con}$ and $-\vec{q}_{con}$ corresponding to the allowed[185] conrotation of the methylene end groups. These lines terminate in two different (enantiomeric) minima. If a substituent is introduced into the third position of cyclobutene these two paths become nonequivalent and we observe the so-called rotational stereoselectivity.[193,196]

If the elementary step of the reaction corresponds to two (or several) equivalent gradient lines connecting two minima the mechanism of the elementary step includes the transformations which the molecular system undergoes along all these equivalent gradient lines (see, for example, Fig. 12).

The mechanism of the elementary step is more complex in the case of the valence isomerisation reaction of the cyclooctatetraene molecule. As can be seen from Scheme 6 there is only one transition state **13** between the four equivalent minima **11a–11d**. The reaction in the chemical system takes place only when the latter is thermally excited to an energy corresponding to the transition state (ignoring the possibility of tunnelling), i.e. it is transferred from the zero vibrational level to an excited energy level located above the transition state (Fig. 14). If there are two equivalent transition states the reaction can take place through either. Therefore in order to induce the isomerisation of the cyclooctatetraene molecule from one of the minima (**11a**) into another (for example, **11b**) the system must be promoted to a vibrational energy level lying above the transition state **13**. However, in this case the system will rapidly become delocalised on this hypersurface with equal probabilities for the four minima **11a–11d**, and it can then relax to the zero vibrational level in each minimum. Therefore in this case the elementary step is described by three gradient lines: **11a** ⇄ **12a** ⇄ **11c**, **11b** ⇄ **12b** ⇄ **11d**, and **12a** ⇄ **13** ⇄ **12b** (see Scheme 6), and hence the mechanism of the elementary step is the totality of the transformations of the system along the three gradient lines. However, if we are concerned only with the inversion of the ring, the mechanism of the elementary step now becomes the totality of the transformations along only one of the lines, **11a** ⇄ **12a** ⇄ **11c** or **11b** ⇄ **12b** ⇄ **11d** (Scheme 18).

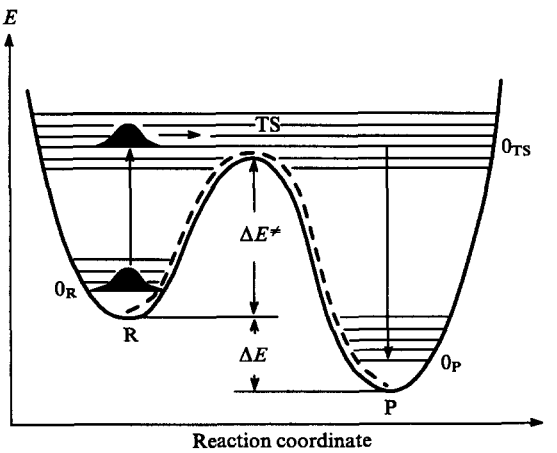
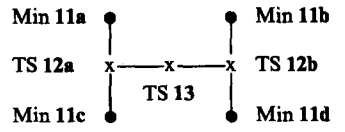


Figure 14. Classical reaction path (broken line joining the minima of the reactant R and of the product P through the saddle point of the transition state TS) and quantum transition (vertical arrows) from the vibrational ground state of the reactant (0_R) to the vibrational state (0_{TS}) lying above the energy of the transition state, and beyond to the vibrational ground state of the product (0_P).



Scheme 18

It is often assumed[61,75,203] that any unimolecular reaction begins along the 'softest mode', i.e. along the vector $\vec{q}_1$ corresponding to the minimum frequency. It is evident from the above discussion that this assertion is not entirely accurate, since in addition to the very large number of secondary gradient lines tangential to the vector $\vec{q}_1$ we have $2(3N-7)$ principal gradient lines tangential to the vectors $\pm\vec{q}_i$ ($i = 2, 3, ..., 3N-6$), which may also contain transition states. Of course, the chemical system can take part in all the reactions corresponding to these transition states, but the number of transition states which may be found on the secondary gradient lines entering a given minimum is still an unsolved problem. Therefore the problem of listing all the reaction mechanism available to a molecular configuration corresponding to a given minimum is also still unsolved. Obviously, the number of such mechanisms must be finite.

As was pointed out above, the chemical system can move away from a minimum only along the appropriate gradient line. This means that it can begin to move from the minimum only along one of the $\vec{q}_i$ vectors ($i = 1, 2, ..., 3N-6$), i.e. the chemical reaction can start only along a normal (collective) mode.[80] The idea of using a normal mode to describe a motion with a large amplitude was stimulated by the discovery by Pitzer and Kemp[204] (in 1937) of the restricted internal rotation in ethane. The idea was later developed and used to explain the mechanism of the internal pseudorotation in cyclopentane[205-209] and other molecules.[13,14,115] The same idea was recently extended to pericyclic reactions in the outstanding studies of Woodward and Hoffmann.[185] The case of unimolecular reactions of an arbitrary type has been discussed by the writer.[80]

The motion of the system from a minimum along a gradient line tangential to one of the $\vec{q}_i$ vectors ($i = 1, 2, ..., 3N-6$) helps us to understand the nature of the departure of the gradient path from the shortest path (in which the reaction follows the shortest path of each atom in the molecular system from the reactants to the products), proposed by Rice and Teller[210] in 1938 (see also Ref. 62). If the direction of the $\vec{q}_i$ vector coincides with that of the shortest distance path the reaction follows this path. However, the gradient path of the reaction may not coincide with the shortest distance path. For example, the transformation of the cyclobutene molecule into the gauche form of 1,3-butadiene (see Fig. 13) follows a path close to the shortest distance path, as can easily be seen by superimposing the structures along the reaction path. In this case the motion of each atom from its initial position (cyclobutene) to the final position (butadiene) is almost a straight line. In contrast to this reaction the elimination of a hydrogen molecule from 1,4-cyclohexadiene (according to MCSCF ab initio calculations in 6-31G and 6-31G** bases)[211] follows a path markedly different from the shortest distance path. As can be seen from Fig. 15, during the reaction the atoms follow fairly complex trajectories strongly different from straight lines. The normal vibration vector, shown by arrows in Fig. 15 and tangential to the reaction path, corresponds to the distortion of the planar structure into a bathtub conformation and does not agree (in this case) with the direction of shortest travel. An interesting characteristic of this process is the observation (in experimental studies of the distribution of vibrational and rotational energy in the products of the elimination reaction)[212] that a hydrogen molecule being removed from the benzene begins to rotate in a plane parallel to the benzene ring, which cannot be explained by the calculated[221] characteristics of the PES. In order to reconcile the experimental[212] and the theoretical data[211] we must postulate a second transition state on the reaction path (the point A in Fig. 15) with a structure of C_{2v} symmetry, corresponding to the rotation of the hydrogen molecule in a plane parallel to that of the benzene ring.

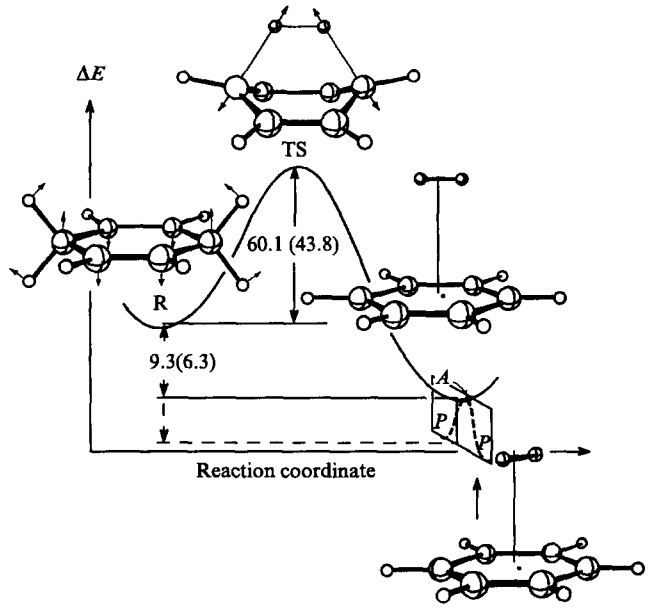


Figure 15. Transformation of the 1,4-cyclohexadiene molecule along the reaction path of the reaction for the removal of a hydrogen molecule according to ab initio calculations[211] (numbers without parentheses, kcal mol^{-1}). Experimental data for the activation barrier[213] and for the heat of the reaction[214] are given (numbers in parentheses). In order to reconcile the calculated PES [211] with the experimental data[212] we must assume that the point A corresponds to the second transition state on the path of the elimination reaction and that this structure is the transition state for the internal rotation of the hydrogen molecule in a plane parallel to the benzene molecule (broken line). The arrows show the components of the normal vibration vector at the minimum and of the transition vector at the saddle point.

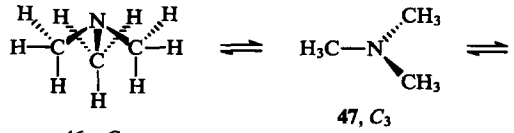
At the second transition state the translational motion of the hydrogen molecule with respect to the benzene becomes a rotational motion. In this case the gradient reaction path becomes analogous to the reaction path proposed in Scheme 2.

This approach also makes clear the nature of the strictly correlated conrotational or disrotational motion of the methylene end groups in the pericyclic ring opening reactions of polyenes,[185] and answers a number of other questions. For example, how does one methylene group at the beginning of the reaction 'sense' that another methylene group has started to move, and how does it establish the direction of this motion so as to align itself correctly with it? Why is the character of this correlated motion often different in similar systems? Answers to these questions can be given relatively simply by using existing data.[80] At a minimum point the molecular system initially has a limited choice of vibrational modes, corresponding only to the conrotational and the disrotational modes of the methylene group (see, for example, the calculations[215] of the rotational spectra of the *cis*- and *gauche*-conformers of 1,3-butadiene). Therefore in this system the gradient path of the reaction begins at a minimum tangentially to the vectors of these modes.

VI. Collective processes

Any single-stage process can be treated as a collective process. The most important collective processes are those consisting in the correlated (coordinated) motion of two or several groups (especially between not covalently bound fragments) with relatively minor changes in the other geometric parameters of the system. Equally important are the conditions under which the independent motion of these groups (multistage reaction) becomes single-stage. Let us make these statements clearer by considering some examples.

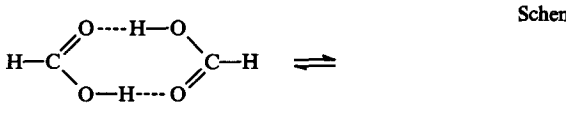
Scheme 19



46a, C_{3v} **47**, C_3 **46b**, C_{3v}

We shall discuss as a first example the inversion reaction of the trimethylamine molecule $(CH_3)_3N$ (Scheme 19). In the ground state this molecule has a C_{3v} symmetry.[216] In the transition structure during the inversion through a planar configuration of N–C bonds surrounding the nitrogen atom the molecule acquires the C_3 configuration. This means that all three methyl groups rotate simultaneously and synchronously during the reaction, so that a collective process of simultaneous and strictly correlated motion of all the stereochemically labile groups can take place in this reaction, i.e. the inversion of the bonds on the nitrogen atom induces a synchronous internal rotation of the methyl groups. A similar inversion process occurs in the $(CH_3)_3O^+$ (see Ref. 217) and the $(CH_3)_3S^+$ cations (see Ref. 216).

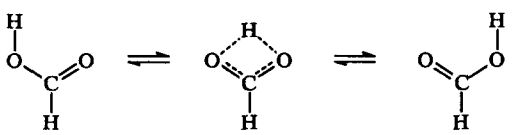
Scheme 20



48a **49** **48b**

We shall discuss as a second example the intermolecular double proton exchange in the dimers of formic acid[163,218,219] and pyrazole,[220–222] and the triple (in the trimer) and the four-fold proton transfer (in the tetramer) of pyrazole[220–222] (Scheme 20). As shown by theoretical and by experimental studies of the formic acid dimer[163,218,219] a double proton transfer takes place simultaneously in this system through the symmetrical transition structure **49** with an activation barrier of ~8 kcal mol^{-1} (see Ref. 163). At the same time the intramolecular transfer of a proton between oxygen atoms (Scheme 21) in the monomer **50** takes place, according to ab initio calculations,[223] with a much higher activation barrier: about 40 kcal mol^{-1}.

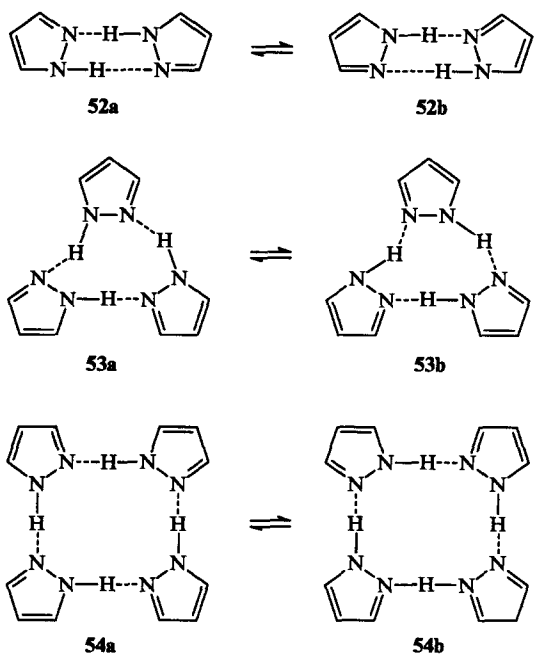
Scheme 21



50a **51** **50b**

Similar studies of the pyrazole dimers,[220,222] trimers,[220] and tetramers[222] showed that fast, reversible low-barrier proton transfer processes are possible in these systems. On the other hand the intramolecular proton transfer in pyrazole, as in formic acid, involves overcoming a substantially higher activation barrier (Scheme 22).

Scheme 22

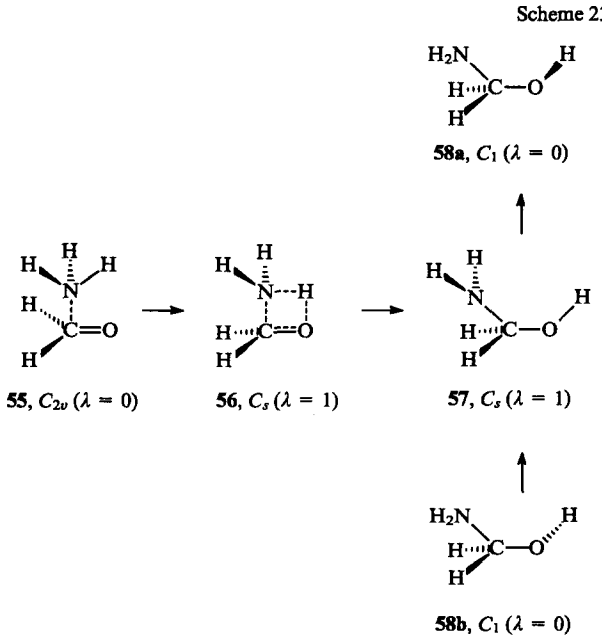


52a **52b** **53a** **53b** **54a** **54b**

According to experimental data[220–222] the rate of the proton transfer reaction in the series of compounds **52**–**54** decreases at first (on going from the dimer **52** to the trimer **53**), and then increases again in the tetramer **54**. This can be ascribed to the replacement of the concerted proton transfer in **52** by a multistage process in **54**.

The low activation barriers to the intermolecular double and triple proton transfer processes in these systems are due to two factors: the almost ideal stereochemical conditions found by the proton transfer[224–226] and the catalytic (acid–base) action of the second hydrogen bond, which greatly assists the reaction.[64]

Scheme 23



58a, C_1 ($\lambda = 0$) **55**, C_{2v} ($\lambda = 0$) **56**, C_s ($\lambda = 1$) **57**, C_s ($\lambda = 1$) **58b**, C_1 ($\lambda = 0$)

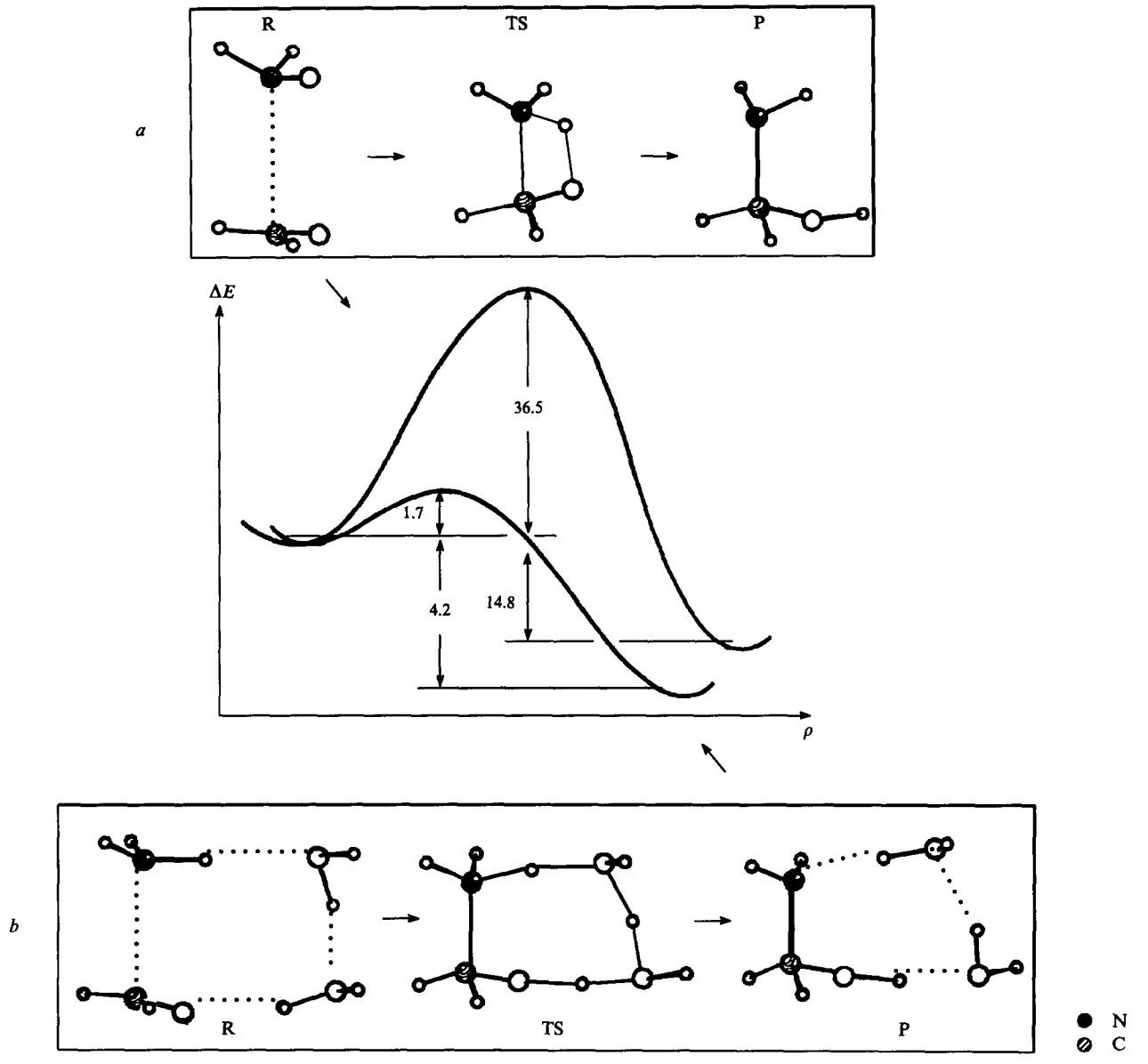


Figure 16. Mechanism of the addition of an ammonia molecule to formaldehyde according to ab initio calculations.[26] (*a*) Not allowing for solvation; (*b*) allowing for solvation by two water molecules. The relative energies are given in kcal mol^{-1}; ρ is the reaction coordinate.

Small differences in the distance between the hydrogen-bonded monomers lead to marked changes in the mechanism of the transfer process. Thus, the transition from the dimer of formic acid[163] to the dimers of formamide and of formamidine converts the proton transfer mechanism from single-stage (synchronous) to multistage (non-synchronous) as a result of the increased length of the H bond.

Our third example is the nucleophilic addition reaction of an ammonia molecule to formaldehyde with formation of aminomethanol and solvation by two water molecules (Scheme 23),[26,227] which is a model of the formation of peptide bonds in proteins.[228] The reaction begins with the formation of the complex **55**, in which the nitrogen atom of the ammonia molecule is oriented towards the carbonyl group. The reaction proceeds by the synchronous motion of all the atoms in the system through the multicentre transition state **56**. The energy profile of the reaction and its geometric evolution are shown in Fig. 16, together with data for the system which allow for the solvation by two water molecules. A comparison of the solvated and the nonsolvated system leads to the following conclusions.

First, in the nonsolvated system the reaction takes place along two gradient lines. Initially, from the pre-reaction complex **55** through the transition state **56** to the following transition state **57**, the system slides along a single gradient line. At the point corresponding to the structure **57** the system passes from the first line to the second, corresponding to the internal rotation of the O–H bond round the C–O single bond. In this way the two enantiomeric forms **58a** and **58b** appear as products in the nonsolvated system. Solvation with two water molecules lowers the initial symmetry C_s of the system to C_1, and the second (enantiomeric) reaction channel disappears.

Second, as the nitrogen atom approaches the carbon atom of the carbonyl group three protons are collectively transferred over the three hydrogen bridges in the system.

Third, in the pre-reaction solvated complex all the constituent single molecules are oriented in such a way that the stereochemical conditions most favourable to four simultaneous reactions[224–226,229–232] are satisfied: the nucleophilic addition to the carbonyl group[229–232] and three proton transfers over the hydrogen bridges.[224–226]

VII. Biological systems

The examples of various chemical reactions examined above have revealed some extremely branched (multichannel) mechanisms. Conversely, chemical reactions in living organisms follow strictly single paths.[228,233-236] This is because all living organisms (including the living cell) are essentially molecular machines,[233,235,236] and (accordingly) they function as machines, in a strictly determined rather than a random way. In this case the 'global' thermodynamics of biochemical processes (in particular the path of the reaction and its energy profile along this path) should be 'machine like'.[235,236]

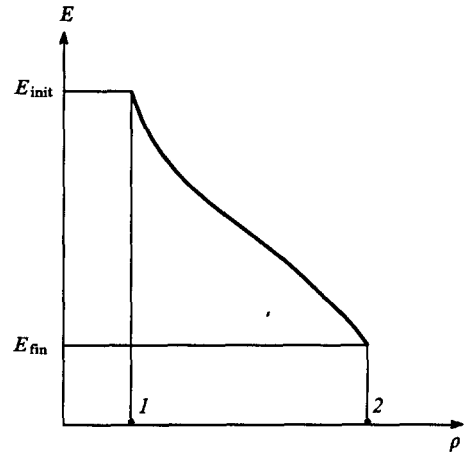


Figure 17. Energy profile of a living organism as a macroscopic body as a function of the internal reaction coordinate ρ. (*1*) and (*2*) are the initial and the final point of the motion along the reaction coordinate respectively. The reaction coordinate ρ is the length along the reaction path constructed in the coordinate system of the centre of mass.

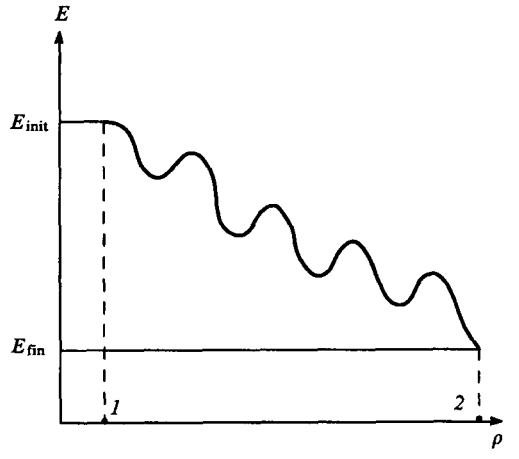


Figure 18. Energy profile of the system of a living organism as the combination of all the biochemical reactions along the reaction coordinate ρ. The points *1* and *2* correspond to those defined in Fig. 17.

The global energy profile of a living system is determined by examining its motion over a small enough time interval, during which the system can be treated as closed.[237] The motion of a system such as a macroscopic body as a whole is determined by the law of energy conservation (the first law of thermodynamics) irrespectively of the internal structure or of the nature of the internal interactions taking place in it.[237] The motion of the body over a small time interval satisfies the inequality

$$E_{init} > E_{fin},$$

where E_{init} and E_{fin} are the total energies of the system at the initial and the final moments. Therefore the dependence of the total internal energy of the system on the internal reaction coordinate (corresponding to a small time interval) is shown as a falling curve (Fig. 17). At the same time, any biological system is a plurality of chemical reactions strictly correlated in time and space. We know that the energy profile of the elementary step of any chemical reaction is defined by the Arrhenius curve.[59,83,238] A very large number of these elementary steps can occur in living cells. If they are mutually indepen-dent[228,238] the overall profile of the biological system consists of the independent profiles of the separate elementary chemical reactions, and it can be represented by the curve shown in Fig. 18. In this respect the profile of biological systems (interpreted as the combined profiles of many chemical reactions) does not coincide with the energy profile of Fig. 17. Thus we meet a difference in principle between the very complex energy profile of processes in biological systems and the energy profile of the macroscopic body (including biological bodies). In order to reconcile the profiles of biosystems (as macroscopic objects and as biochemical systems consisting of chemical reactions following microscopically separate paths) we must assume that the profile shown in Fig. 17 consists of a large number of separate parts corresponding to separate chemical reactions in the biosystem. This is possible if the final point of the previous reaction occurs after the activated barrier of the subsequent reaction, i.e. if the energy profile can be represented by the curve shown in Fig. 19. Only this reconciliation of the profiles of the elementary chemical reactions in the biological system can allow the development of functional systems such as molecular machines. Of course, this description is strictly schematic and oversimplified, and it cannot be offered as the final picture, but the arguments used above make clear the essential difference between chemical reactions and their biochemical analogues in the living organism. This difference suggests one possible direction for further studies of collective reactions.

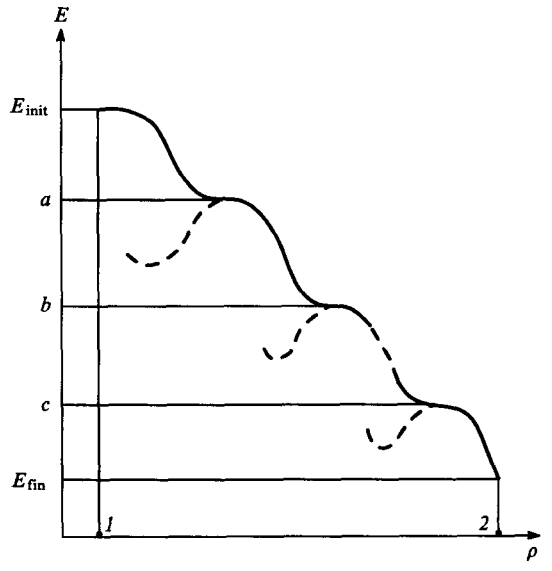


Figure 19. Full energy profile (thick line) of the system of a living organism as the combination of separate biochemical reactions (broken line) strictly correlated in space and time. Each reaction terminates at a point lying beyond the transition state of the 'next' reaction. E_{init} denotes the 'first' reaction (corresponding to the point *1* on the reaction coordinate ρ), which terminates at the point *a*. The second reaction begins at this point, and terminates at the point *b*. The point *c* denotes the initial point of the 'next' reaction, which terminates at the point *2*.

VIII. Conclusion

The stereochemical paths (mechanisms) of the elementary steps of the main types of chemical reaction, of which relatively few have so far been identified,[64,185,186,232] have been studied in depth both experimentally and theoretically. Many workers[4,13,14,22,64,185,196,202,230] have successfully determined the stereochemical trajectories of their reaction paths, and the electronic nature of the driving force is now understood for most reactions. However, in practice chemical reactions are usually collective processes in a multicomponent system with a simultaneous or strictly correlated (relay mechanism) sequence of motions over the whole system. Biological reactions involving enzymes are a special case of these reactions. Therefore, in order to understand the nature of enzyme reactions we must progress from the study of the PES of simple systems to the study of the PES of chemical systems which model the course of several reactions at the same time. This calls, in turn, for the development of new methods of analysis of the topological structure of multidimensional PES, for the further development of nonempirical and semiempirical quantum-chemical methods of calculation, and lastly for an increase in the power and speed of response of the computers used in these studies.

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