Downloaded from rstb.royalsocietypublishing.org

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

# Chemical Reaction Paths

J. D. Dunitz

*Phil. Trans. R. Soc. Lond. B* 1975 **272**, 99-108
doi: 10.1098/rstb.1975.0073

**Email alerting service**

Receive free email alerts when new articles cite this article - sign up in the box at the top right-hand corner of the article or click **here**

To subscribe to *Phil. Trans. R. Soc. Lond. B* go to: **http://rstb.royalsocietypublishing.org/subscriptions**

This journal is © 1975 The Royal Society

Downloaded from rstb.royalsocietypublishing.org

*Phil. Trans. R. Soc. Lond.* B. **272**, 99–108 (1975) 
*Printed in Great Britain*

# Chemical reaction paths

By J. D. Dunitz, F.R.S.
*Organic Chemistry Laboratory, Swiss Federal Institute of Technology (E.T.H.),*
8006 *Zürich, Switzerland*

When two molecules react with one another their mutual approach and subsequent structural reorganization have to follow more or less along a minimum energy pathway in the multidimensional parameter space that defines the structure of the reacting system. Information about such paths can be obtained, in principle, by examining how the structural parameters of certain molecules or parts of molecules change in response to perturbations connected with different crystal or molecular environments. In some cases, striking correlations between independent structural parameters describing molecular sub-systems frozen in different environments have been detected. This makes it possible to arrange the individual structures in a sequence that corresponds, in a general sense, to the course of structural changes expected to occur in a chemical reaction. In this way, reaction paths for several prototypal chemical reactions ($S_N1$, $S_N2$, nucleophilic addition to carbonyl groups) have been derived.

## Molecular potential energy surfaces

The concept of the potential energy hypersurface is almost indispensable for discussing chemical reactions. Stable molecules correspond to potential energy minima, molecular transformations to the passage of a representative point, describing the relative displacements of the nuclei, from one potential energy minimum to another. Actually we deal with very large numbers of molecules, each of which takes a somewhat different trajectory, depending on the exact details of its random encounters with other molecules. Nevertheless, these trajectories tend to be concentrated along the energy valleys that connect the minima over the lowest pass between them, and we can refer to these valleys as reaction paths or minimum energy paths. A knowledge of the minimum energy path for a given reaction would tell us how molecules have to approach one another for that reaction to proceed and how changes in different structural parameters are coupled during the course of the reaction. However, it is very difficult to obtain this information, either from experiment or from theoretical calculations. Needless to say, the changes in the reacting molecules themselves cannot be followed since each molecule carries out its structural transformation in such a short time interval that it cannot be observed directly.

On the experimental side, we can determine the structures of stable molecular species by diffraction methods, we can assess the relative depths of the corresponding energy minima from equilibria or from thermochemical measurements, and we can estimate the relative height of the lowest pass separating these minima from kinetic studies. For a few very simple or highly symmetrical molecules, the behaviour of the potential energy hypersurface close to the equilibrium structure can be derived from analysis of vibrational spectra. All these pieces of information are essential but they are inadequate even for a qualitative description of the minimum energy path.

In principle, potential energy surfaces can be obtained from quantum mechanical calculations based on the Born–Oppenheimer approximation, according to which the total potential



The Royal Society is collaborating with JSTOR to digitize, preserve, and extend access to *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences.* www.jstor.org

Downloaded from rstb.royalsocietypublishing.org



energy of an assemblage of nuclei and electrons in a given electronic state depends only on the relative positions of the nuclei. However, there are formidable difficulties in practice, and the computational outlay soon becomes prohibitive with increasing complexity of the system. The best known example of a calculated potential energy surface is surely for the system consisting of three hydrogen atoms where the nuclei are constrained to lie in a line. A discussion of the qualitative features of this surface is to be found in any book on transition-state theory, but the main points may be mentioned here very briefly.

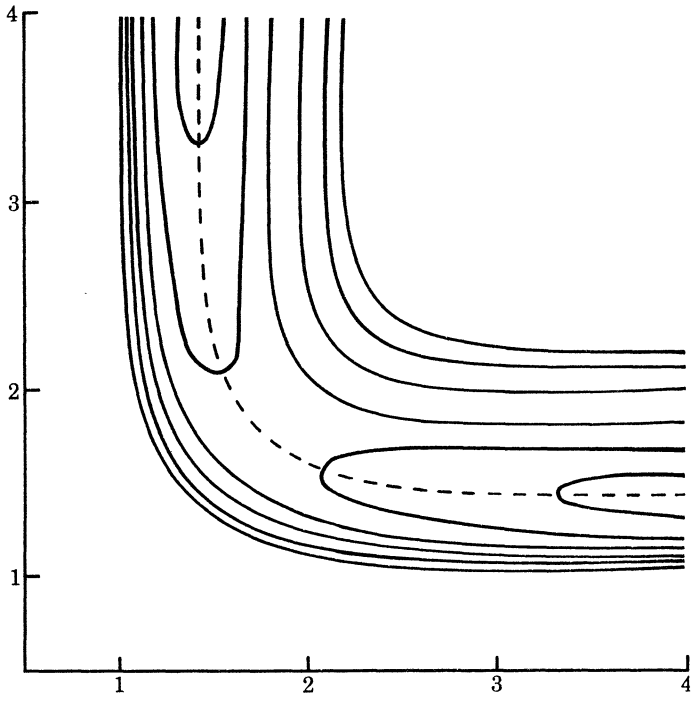



FIGURE 1. Potential energy surface for linear $H_3$ system, drawn from data calculated by Liu (1973). Contour lines are drawn at energy intervals of 0.01 a.u.

The profiles along the top and the right hand sides of figure 1 correspond to the potential energy of an $H_2$ molecule as a function of internuclear distance, with the third hydrogen atom sufficiently distant that its interaction with the molecule can be neglected. As this hydrogen begins to approach the $H_2$ molecule, the potential energy of the system increases, but there is one path along which the energy increase is less than that in other directions. The point of highest energy along this path corresponds to the transition state for the reaction H—H + H ↔ H + H—H.

## LINEAR THREE-CENTRE REACTIONS

Figure 2 shows the experimental correlation between the two I. . .I distances in the linear triiodide ion, as observed in several different crystal structures. Bent (1968) noted that this hyperboloid curve may be presumed to show, approximately, the changes that occur in the course of the reaction $I^- + I—I \leftrightarrow I—I + I^-$. Indeed, the similarity between this curve and the minimum energy path of figure 1 is quite remarkable, considering that one curve refers to the result of a theoretical calculation for an isolated system containing three electrons, the other to

Downloaded from rstb.royalsocietypublishing.org



an experimental correlation for a system containing 160 electrons in a series of tightly packed crystalline environments with strong perturbations arising from the presence of the neighbouring counter-ions. Very similar experimental correlations are obtained for other linear or nearly linear triatomic systems, such as the S—S . . . S grouping in thiothiophthenes and the O—H . . . O grouping in various hydrogen-bonded aggregates.

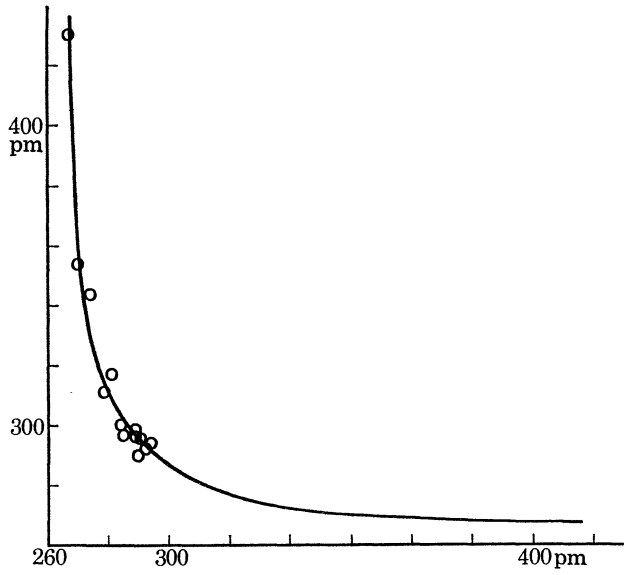



FIGURE 2. Plot of long against short I . . . I distances in $I_3^-$ anions observed in several different crystal structures. The smooth curve represents the function $10^{-(d_1-267)/c}+10^{-(d_2-267)/c}=1$ with $c=(290-267)/\lg 2=76.5$ pm. The distances 267 pm and 290 pm correspond to the isolated $I_2$ molecule and the symmetric $I_3^-$ anion, respectively.

The lengthening of the I—I distance on passing from the diatomic $I_2$ molecule to the symmetrical $I_3^-$ anion is 23 pm, and the corresponding lengthening for other types of bonds is also often close to this value. For example, the O—H distance is 99 pm in $H_2O$ and 121 pm in a symmetrical hydrogen bond, the F—H distance is 91 pm in HF and 113 pm in $[F \ldots H \ldots F]^-$, the S—S distance is 208 pm in sulphur and about 231 pm in symmetrical thiothiophthenes. For the linear $H_3$ molecule the corresponding lengthening is 18.5 pm, according to recent calculations by Liu (1973).

In a paper dealing with interatomic distances in metals Pauling (1947) proposed that the length of a fractional bond is related to that of a single bond by the relation, $d(n)—d(1) = -c \lg n$, where $n$ was called the bond number. The constant $c$ was assigned the value 60 pm, but it can be expected to vary, depending on the nature of the atoms involved. For discussing the linear triatomics, we adopt the Pauling relation with the additional assumption that the sum of the two bond numbers equals unity for all related pairs of interatomic distances. This leads to the analytic expression

$$10^{-\Delta d_1/c}+10^{-\Delta d_2/c}=1,$$

where $\Delta d_1$ and $\Delta d_2$ are related bond distance increments and $c=\Delta d'/\lg 2$, with $\Delta d'$ the bond distance increment in the symmetrical structure ($n=\frac{1}{2}$). The smooth curve in figure 2 represents this function with $\Delta d'=23$ pm ($c=76$ pm) and reproduces the observed correlation extremely well. Similarly good agreement is obtained for the other linear triatomics for which

Downloaded from rstb.royalsocietypublishing.org



data are available. For the $H_3$ system the sum of the bond numbers is found to lie within the range 1.00 to 1.02 for all points along Liu's calculated minimum energy path.

## The principle of structural correlation

These results show that, at least for several linear triatomics, the curves describing the correlation between interatomic distances observed in different crystal environments have a remarkably close resemblance to the calculated reaction path for the $H_3$ system. Moreover, the curves can be reproduced in good approximation by simple analytical functions containing only one adjustable parameter, which can be assigned by assuming that some bonding property (the sum of the Pauling bond numbers) remains invariant throughout the 'reaction'. There is no theoretical justification for this assumption, which was also used by Johnston (1960) as basis for his b.e.b.o. (bond energy–bond order) method of estimating the form of the reaction path for hydrogen transfer.

For most chemical reactions the minimum energy path is not known. Imagine that by making suitable changes in the educt or product molecules, we could move the corresponding potential energy minimum a little along the reaction path. By observing the structural parameters of the sequence of increasingly deformed molecules we might be able to describe the main features of the reaction path in question. This approach has been used to obtain information about the reaction path for cis-trans isomerization of the amide group (Dunitz & Winkler 1975). However, in general we are unable to vary the molecular structure or environment in the systematic way that would be necessary to 'observe' a sufficient number of sample points along the reaction coordinate.

As an alternative, we might try to search for correlations among the available experimental structural data for a given molecule or molecular fragment in different environments. If such correlations can be found between two or more independent parameters describing the structure of the system in question, then the correlation function can be regarded as a good approximation to a minimum energy path in the parameter space describing the structure of that system; moreover, if the pattern of structural changes can be identified in a general way with that expected to occur in the course of a chemical reaction, then the path found from such experimental data should be a fair approximation to the corresponding reaction path. The actual equilibrium arrangement of atoms found in any given environment obviously depends on a complicated interplay of intra- and inter-molecular forces that is rarely understood in detail, but it seems reasonable to expect that any smooth sequence of changes in the structure of a subunit will occur along an energy valley in its parameter space – in other words, that the subunit will tend to deform along the path of least resistance. The scatter of sample-points from the smooth curve may well arise from the different perturbations that act on our subunit in its different environments, as well as from experimental inaccuracies, and we have to hope that this scatter will be averaged out if sufficient sample-points are available.

During the last two years we have been using this approach to try to determine reaction pathways for several types of chemical reactions – $S_N2$ type (Bürgi 1973), $S_N1$ type (Murray-Rust, Bürgi & Dunitz 1975), nucleophilic addition/elimination reactions at carbonyl groups (Bürgi, Dunitz & Shefter 1973*a*, 1974; Bürgi, Dunitz, Lehn & Wipff 1974), and the cycloheptatriene/norcaradiene type of ring closure reaction (Bürgi, Shefter & Dunitz 1975). Muetterties & Guggenberger (1974) have used essentially the same approach to delineate the

Downloaded from rstb.royalsocietypublishing.org



reaction path for isomerizations of trigonal bipyramidal molecules. Here, we review some of the results for the mucleophilic addition/elimination reaction.

## Nucleophilic addition to a carbonyl group

Nucleophilic addition to the carbonyl group is one of the most important types of chemical reaction, being involved in the formation of acetals, ketals, etc. and in the formation and interconversions of carboxylic esters, amides, and anhydrides. Countless crystal structure analyses have provided an enormous body of information about the detailed structures of such compounds and it has also revealed several examples of intra- and inter-molecular 'non-bonded' interactions between nucleophilic centres and carbonyl groups. Here we take the view that these examples represent points along the reaction coordinate that have been 'frozen in' by the various constraints or other factors operating in the molecule or crystal in question.

Strong transannular interactions between amino and carbonyl groups in natural product molecules containing medium rings were proposed many years ago and subsequently confirmed by infrared spectroscopy (see Leonard 1956, for a review). Several examples of unusually short, transannular N . . . C=O distances were discovered by crystal structure analysis, and it was noted by Birnbaum (1972) that in clivorine, where the N . . . C distance is only 199 pm, about 100 pm shorter than the sum of van der Waals radii, the carbonyl group is no longer coplanar with its substituents but is appreciably distorted towards tetrahedral coordination. An initial survey (Bürgi *et al.* 1973*a*), based on structural information available for six molecules containing N . . . C=O distances in the range from 150 to 290 pm, showed that when the relevant parts of the structures were projected on to the NCO plane (an approximate mirror plane in all cases) as in figure 3, the resulting sets of points (*A*, *G*, *H*, *K*, *L*, *M*) gave a rather clear picture of the course of geometric changes that occur during the addition reaction. As the nucleophile approaches the carbonyl C atom, the plane containing this atom and its two alkyl substituents bends away, and the C=O distance increases. The experimental points leave no doubt that the approach of the nucleophile is along a direction at approximately 109° to the C=O bond and certainly not perpendicular to it. Figure 3 contains additional points obtained from new data that have become available since the initial survey was carried out. The additional points do not alter the general picture although they affect some of its details. The lone-pair orbital of the approaching nitrogen atom can be assumed to lie roughly along the local threefold axis of the tertiary amino group. For the longer N . . . C distances this direction is rather variable but for the shorter ones the lone-pair direction is virtually coincident with the N . . . C direction.

In some of the molecules included in our survey, an optimal direction of approach of the nucleophile and its electron-pair is hindered by geometric restrictions associated with the nature of the molecular skeleton that carries the interacting groups. This is most obvious for the 1,8-disubstituted naphthalene derivatives. In most 1,8-disubstituted naphthalenes repulsion between the substituents splays the exocyclic bonds outwards so as to increase the distance between the substituents to about 300 pm. When one substituent is a nucleophile, the other an electrophilic carbonyl group, the nucleophile–electrophile distance might be expected to be considerably less than 300 pm. However, in the undistorted naphthalene skeleton with 120° angles at the 1,8-positions, the N . . . C=O angle would be 90° instead of *ca.* 109° and the nitrogen lone pair is not directed towards the electrophilic carbon atom. Other conditions for

Downloaded from rstb.royalsocietypublishing.org



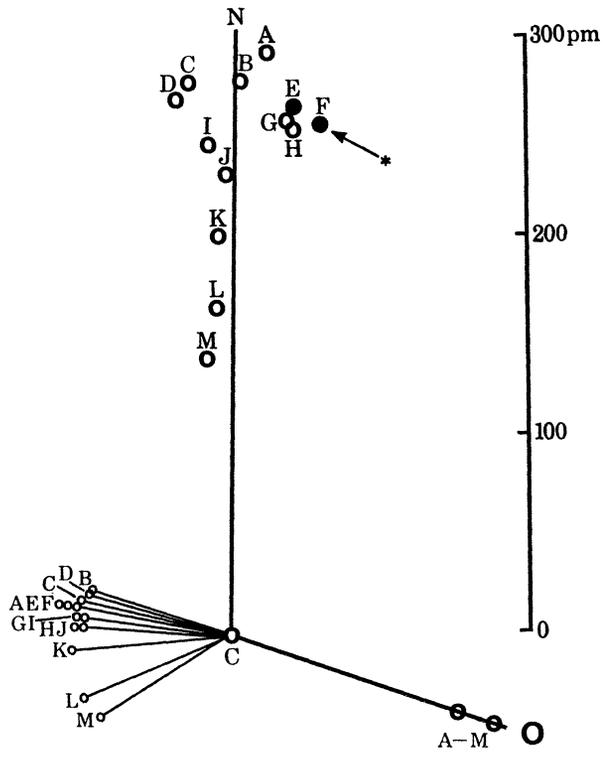
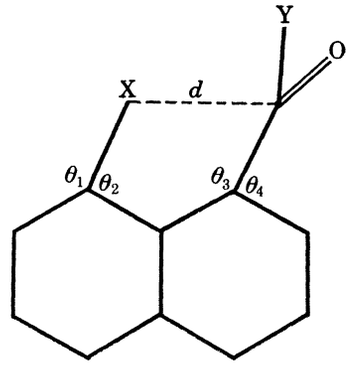



FIGURE 3. Relative positions of C, N, O atoms and of RR′C plane in molecules showing N...C=O interactions. The labelled points refer to: *A*, methadone (Bürgi *et al.* 1973*b*); *B*, 1-*p*-tolyl-1-azacyclooctane-5-one (Kaftory 1974); *C*, *D*, 1,5-dinitro-3-methyl-3-azabicyclo[3.3.1]nonan-7-one, monoclinic and orthorhombic forms (Kaftory 1974); *E*, 1-naphthoic acid-8-*N*,*N*-dimethylamine (Schweizer & Kaftory 1974); *F*, 1-naphthoic acid methyl ester-8-*N*,*N*-dimethylamine (Schweizer & Kaftory 1974); *G*, cryptopine (Hall & Ahmed 1968*a*); *H*, protopine (Hall & Ahmed 1968*b*); *I*, 11-methyl-11-azabicyclo[5.3.1]undecane-4-one (Kaftory 1974); *J*, senkerkine (Birnbaum 1974); *K*, clivorine (Birnbaum 1972); *L*, retusamine (Wunderlich 1967); *M*, *N*-brosyl-mitamycin A (Tulinsky & van der Hende 1967). The arrow indicates the relative displacement of the N atom (black circles) associated with bending of the exocyclic bonds in the two naphthalene derivatives (see figure 4).




| X | Y | $\theta_1$° | $\theta_2$° | $\theta_3$° | $\theta_4$° | *d*/pm |
|---|---|---|---|---|---|---|
| $OCH_3$ | $CH_3$ | 124 | 116 | 126 | 115 | 261 |
| $OCH_3$ | OH | 125 | 113 | 123 | 116 | 256 |
| $N(CH_3)_2$ | $OCH_3$ | 124 | 117 | 122 | 118 | 259 |
| $N(CH_3)_2$ | OH | 122 | 118 | 124 | 116 | 261 |

FIGURE 4. Distortion of exocyclic bonds in 1,8-disubstituted naphthalene derivatives where one substituent (X) is a nucleophile, the other a carbonyl group.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org



optimal interaction are that the mean plane of the RR′CO grouping should be normal to the plane of the naphthalene skeleton and the dimethylamino grouping should be bisected by the naphthalene plane. The crystal structure analysis of 1-naphthoic acid methyl ester-8-*N*,*N*-dimethylamine (Schweizer & Kaftory 1974) shows that the C1—C bond is splayed outward, the C8—N bond inward to give a N . . . C distance of 259 pm (only slightly larger than the C1 . . . C8 distance of 251 pm) and an N . . . C=O angle of 100° (figure 4). In other words, the usual pattern of bond angles is distorted in such a way as to bring the nitrogen into a more favourable position for nucleophilic attack on the carbonyl group than is possible in the undistorted molecule. Very similar distortions are also found in analogous molecules with a methoxy group replacing the amino group in the 1-position. The 1-naphthoic acid-8-dimethylamine is interesting because the crystal contains two independent molecules in the asymmetric unit. One of these molecules shows the same pattern of bond angle distortions as mentioned above (figure 4), but the other shows both bonds splayed outward, with the carboxyl group in the naphthalene plane rather than perpendicular to it. The explanation is, of course, that the crystal is actually a 1:1 molecular compound of the amino acid, which shows the N . . . C=O interaction, and the corresponding zwitterion, which does not.

The reverse decomposition of the tetrahedral addition complex should proceed along the same path as the addition reaction, and evidence for this comes from correlations (Bürgi, Dunitz & Shefter 1974) between appropriate linear combinations of bond lengths and bond angles in tetrahedral sub-units with two geminal C—O bonds (diols, ketals, hemiketals, acetals, hemiacetals). In cases where the two C—O bond lengths are different, there is a significant correlation between the antisymmetric stretching and bending distortions of the two C—O bonds. This correlation is such as to suggest that in the decomposition of a tetrahedral intermediate the leaving group X does not depart along the initial direction of the C—X bond. Instead, as the C—X bond stretches and the other bond, C—Y, contracts, a coupling between the antisymmetric stretching and bending coordinates causes the C—Y bond to move towards the RCR′ plane and simultaneously adjusts the departure direction of X to maintain an approximately tetrahedral XCY angle.

The picture of the reaction path for nucleophilic addition to carbonyl (figure 3) has been confirmed in some respects and extended in others by non-empirical quantum mechanical calculations for the model system $H_2CO + H^- \rightarrow CH_3O^-$, corresponding to addition of the simplest nucleophile, hydride ion, to formaldehyde to give methanolate anion (Bürgi, Lehn & Wipff 1974; Bürgi, Dunitz, Lehn & Wipff 1974). The initial approach of the hydride ion is along the HCH bisector (ion-dipole interaction) but at $H^-$ . . . C distance of about 300 pm the minimum energy path starts to curve out of the formaldehyde plane. When the $H^-$ . . . C distance is approximately 250 pm, the $H^-$ . . . C=O angle has changed from 180° to about 125°. Finally, as the hydride ion approaches towards the bonding distance, changes in the structure of the formaldehyde molecule occur that are very similar to the changes depicted in figure 3, and the energy valley becomes increasingly steeper and narrower, corresponding to the strongly preferred direction of approach that was inferred from the experimental correlations.

Figure 3 shows that the out-of-plane displacement of the carbon atom ($\Delta$) increases as the N . . . C distance ($d_1$) decreases. In view of our earlier comments on the use of the Pauling relation for describing the minimum energy pathways for linear three-centre reactions, it is rather interesting that the experimental $d_1$, $\Delta$ values for the nucleophilic addition reaction

Downloaded from rstb.royalsocietypublishing.org



(figure 5) lie close to the logarithmic curve

$$d_1 = -139.0 \lg \Delta + 104.9 \text{ pm},$$

where the constants were obtained by least squares regression. [This correlation is based on more extensive experimental data than the one given in our earlier study (Bürgi *et al.* 1973*a*).] A maximum value of $\Delta$ is obtained when $d_1$ equals the C—N single bond distance, for which Birnbaum (1974) has suggested the value 150 pm. Substitution now yields $\Delta_{max} = 47.4$ pm, so that the above function can be rewritten

$$d_1 = -139.0 \lg |(\Delta/\Delta_{max}) + 150 \text{ pm} \quad \text{or} \quad \delta d_1 = -139.0 \lg |(\Delta/\Delta_{max}) = -c \lg n$$

assuming that the Pauling relation is valid here. For the two extreme cases, $\Delta = 0$ and $\Delta = \Delta_{max}$, we obtain $n = 0$ and $n = 1$, respectively. However, we are still free to set $n$ equal

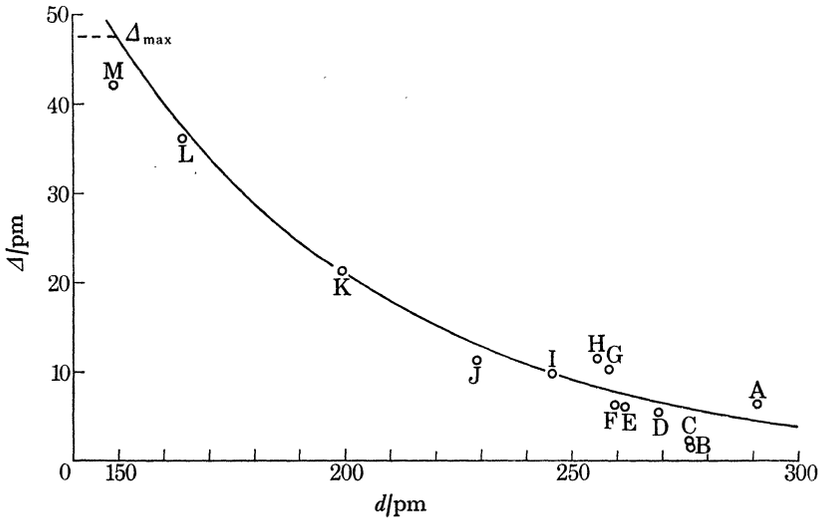



FIGURE 5. Correlation plot of out-of-plane displacement ($\Delta$) against N...C=O distance ($d$) for molecules showing N...C=O interactions. The labelled points refer to the same molecules as in figure 3. The smooth curve is the function $d = -139.0 \lg \Delta + 104.9$ pm.

to $\Delta/\Delta_{max}$ raised to any positive power. If we assume that the sum of the C=O and C...N bond numbers remains invariant in the course of the nucleophilic addition reaction we obtain for the C—O bond distances

$$d_2 = -c \lg (2-n) + 142.6 \text{ pm}.$$

Unfortunately, in this case we know neither the multiplicative constant nor the bond numbers of the N...C bonds. The observed C—O distances tend to cluster around 121–122 pm, except for the extreme cases (points *K*, *L*, *M* in figure 3) where $\Delta$ is approaching $\Delta_{max}$, which suggests that the dependence of $n$ on $(\Delta/\Delta_{max})$ is nonlinear. A second power dependence seems to reproduce the observed trend, but there is of course, no good reason, apart from mathematical convenience, for taking an integral power.

Structural data for O...C=O interactions (oxygen as nucleophile) are much more extensive than for N...C=O interactions, but the picture that emerges is not so clear, mainly because the O...C=O interactions are weaker and more sensitive to the effect of perturbations from the environment. Although observed N...C distances cover the whole range from about 150 pm (covalent bonding) to about 300 pm, there is a pronounced gap between about 160 and 260 pm in the distribution of O...C distances. This gap may be

Downloaded from rstb.royalsocietypublishing.org



due to an unfortunate choice of examples, but it may also occur because the O . . . C=O interaction energy is not large enough to give equilibrium structures in the intermediate region. In spite of the scatter and incompleteness of the data, it is still possible to discern certain similarities and differences between O . . . C=O and N . . . C=O interactions. With oxygen as nucleophile, the angle of approach tends to lie in the range 90–110°, but it is not nearly as constant as in the N . . . C=O examples. Similarly, the out-of-plane displacement of the carbon atom tends to increase with decreasing O . . . C distance, but an averaged curve would lie well below the N . . . C=O curve (figure 5) for $d > 260$ pm. All this seems to fit in with the lower nucleophilicity of oxygen compared to nitrogen.

## Some general comments

We have no way of proving that the smooth curves drawn in figures 2 and 5 actually represent minimum energy paths. It is a plausible interpretation, which we might as well accept as a working hypothesis. Strictly speaking, we should make a distinction between the minimum energy path of an isolated system and the path which maps the response of this system to an external force. The response path is actually the projection of a minimum energy path (in the hyperspace of a more complex system) on the hyperspace of the isolated system and it may be more relevant to the chemical reaction path than the minimum energy path of the isolated system. In drawing conclusions from structural correlations this distinction becomes blurred because of our ignorance of the different perturbing forces that influence the system in its many different environments, so we have tended to use the terms minimum energy path and reaction path more or less indiscriminately. The interactions that we ignore here, those between the system and its different crystal environments, are in any case roughly analogous to those that occur during chemical reactions in solution. However, even if we accept the interpretation of the smooth curves as reaction paths the energy variation *along* the paths cannot be inferred from the structural data alone.

There are some obvious similarities between our approach and that of the protein crystallographer who hopes to obtain information about the mechanisms of enzymatic reactions by studying the structures of a series of related enzymes with various substrates. In both cases the reaction path is, strictly speaking, unobservable, but in both cases it is assumed that this path can be mapped from observations on a sequence of equilibrium structures that are regarded as being 'frozen in' along the path. Our picture (figure 3) of the reaction path for nucleophilic addition to carbonyl seems to fit in very well with results obtained for serine proteases and their complexes with inactive substrates and inhibitors. The first step in the hydrolysis of the peptide bond is believed to be the attack of the serine-195-$\gamma$-oxygen on the carbonyl group of the substrate to give a tetrahedral intermediate or transition state. As Huber (1973, private communication) has pointed out, the changes in the position of this oxygen atom relative to the substrate in several serine proteases and their inhibitor complexes follow a path roughly similar to the one derived from our structural correlations.

The importance of the relative orientation of reactant molecules has also emerged from kinetic studies of Storm & Koshland (1972), who showed that the rate of lactonization of hydroxy acids can be enormously accelerated when the two groups are juxtaposed in a favourable orientation. The preferred angle of approach of the nucleophile inferred from these studies is about 98°; our studies suggest that it should be somewhat larger.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org



The minimum energy paths derived for several reactions from structural correlations or from theoretical calculations can be expressed by simple analytical functions containing only a few adjustable parameters. These can be assigned by recourse to rather primitive assumptions, i.e. that the sum of the Pauling 'bond numbers' remains invariant along the reaction path. It is difficult to know how far this is a matter of curve-fitting and numerology, but one cannot avoid the feeling that it might point to some underlying principle. To a first approximation the minimum energy path for reactions of low activation energy (the only ones we are concerned with) can be regarded as a path of nearly constant energy. If such reactions involve bond breaking and formation, any loss of energy in stretching the bond to be broken must be compensated by a comparable gain in energy from partial formation of the new bond. The minimum energy path is then the path of constant binding energy, and it seems remarkable that this invariance property can be expressed as an invariance of sums of Pauling bond numbers. These quantities lack any theoretical basis, they are defined purely in terms of interatomic distance increments, but they seem to be a useful crutch for deriving analytical functions that represent the observed correlations. Perhaps a theoretical justification for this will be discovered some day.

## References (Dunitz)


Bent, H. A. 1968 *Chem. Rev.* **68**, 587–648.
Birnbaum, G. I. 1974 *J. Am. chem. Soc.* **96**, 6165–6168.
Birnbaum, K. B. 1972 *Acta Crystallogr.* B **28**, 2825–2833.
Bürgi, H. B. 1973 *Inorg. Chem.* **12**, 2321–2325.
Bürgi, H. B., Dunitz, J. D. & Shefter, E. 1973*a* *J. Am. chem. Soc.* **95**, 5065–5067.
Bürgi, H. B., Dunitz, J. D. & Shefter, E. 1973*b* *Cryst. Struct. Commun.* **2**, 667–672.
Bürgi, H. B., Dunitz, J. D. & Shefter, E. 1974 *Acta Crystallogr.* B **30**, 1517–1527.
Bürgi, H. B., Dunitz, J. D., Lehn, J. M. & Wipff, G. 1974 *Tetrahedron* **30**, 1563–1572.
Bürgi, H. B., Lehn, J. M. & Wipff, G. 1974 *J. Am. chem. Soc.* **96**, 1956–1957.
Bürgi, H. B., Shefter, E. & Dunitz, J. D. 1975 *Tetrahedron* **31** (in press.)
Dunitz, J. D. & Winkler, F. K. 1975 *Acta Crystallogr.* B **31**, 251–263.
Hall, S. R. & Ahmed, F. R. 1968*a* *Acta Crystallogr.* B **24**, 346–355.
Hall, S. R. & Ahmed, F. R. 1968*b* *Acta Crystallogr.* B **24**, 337–346.
Johnston, H. S. 1960 *Advan. Chem. Phys.* **3**, 131–170.
Kaftory, M. 1974 Unpublished results.
Leonard, N. J. 1956 *Rec. Chem. Progr.* **17**, 243–257.
Liu, B. 1973 *J. Chem. Phys.* **58**, 1925–1937.
Muetterties, E. L. & Guggenberger, L. J. 1974 *J. Am. chem. Soc.* **96**, 1748–1756.
Murray-Rust, P., Bürgi, H. B. & Dunitz, J. D. 1975 *J. Am. chem. Soc.* **97**, 921–922.
Pauling, L. 1947 *J. Am. chem. Soc.* **69**, 542–553.
Schweizer, W. & Kaftory, M. 1974 Unpublished results.
Storm, D. R. & Koshland, D. E. 1972 *J. Am. chem. Soc.* **94**, 5805–5825.
Tulinsky, A. & van der Hende, J. H. 1967 *J. Am. chem. Soc.* **89**, 2905–2911.
Wunderlich, J. A. 1967 *Acta Crystallogr.* B **23**, 846–855.


PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES