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Chemical Reaction Paths. IV. Aspects of O···C=O Interactions in Crystals

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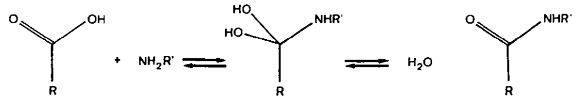
Structural data pertaining to short O···C=O contacts in crystals have been examined with the aim of finding correlations between the various geometrical parameters involved. It is found that for O···C=O distances shorter than 3 Å the carbon atom is displaced from the plane of the carbonyl group (with substitutents) towards the nearby oxygen atom. The displacement tends to increase as the O···C distance decreases. The O···C=O angles show considerable scatter but they tend to lie in the range 100–110°. For tetrahedral carbon atoms of the type $R_2C(OR)_2$ differences in C–O bond distances can be correlated with differences in RCO angles. The observed correlations are discussed in terms of incipient chemical reactions, here addition of a nucleophile to a carbonyl group and the reverse breakdown of the tetrahedral species. Some possible inferences for the interpretation of solid-state and enzymatic reactions are mentioned.

Nucleophilic addition is one of the basic reactions in organic chemistry. It is responsible for the formation and hydrolysis of peptides, carboxylic acid esters and anhydrides, acetals and hemiacetals, ketals and hemiketals. The general course of the reaction is shown below for the formation of an amide:



(I) (II) (III)

The nucleophilic lone pair of an amine ($R'NH_2$) attacks the electrophilic carbon of the carboxylic acid function (I) to form a tetrahedral intermediate or transition state (II), which then eliminates a molecule of water to yield the amide (III). The reverse reaction involves nucleophilic attack by H_2O on the amide (III) to give the tetrahedral intermediate or transition state, followed by elimination of an amine. Although the general mechanism of this class of reaction has been recognized for many years the details of the sequence of structural changes (the reaction path) have remained obscure through their inaccessibility to experimental investigation and the practical difficulties involved in making quantum mechanical calculations on model systems of such complexity.

In a previous paper (Bürgi, Dunitz & Shefter, 1973) we have analysed structural data pertaining to intramolecular N···C=O interactions observed in six crystal structures and have shown that for decreasing N···C distance, the carbonyl carbon is increasingly displaced from the plane of its three ligands towards N and the C–O distance increases. These changes parallel the sequence of structural changes presumed to occur during a nucleophilic addition reaction and may therefore be taken as an experimental basis for mapping the reaction path. The general idea is to select closely similar subunits from a wide variety of structural data, to correlate observed changes in those structural parameters that describe the subunit, and to investigate whether these structural changes correspond to our knowledge or intuition concerning the course of some chemical reaction (Bürgi, 1973; Bürgi, Dunitz & Shefter, 1973). Although the equilibrium arrangement of atoms occurring in a crystal structure depends on a complicated interplay of inter- and intramolecular forces that are rarely understood in detail, it seems a useful working hypothesis to assume that any observable sequence of changes in the structure of such a subunit will occur along a potential-energy valley in the limited parameter space defining that subunit – even when, or perhaps especially when, the observations pertain to widely different environments. However, the subunit of interest is usually only a small part of the crystal structure and the interactions relevant to the chemical reaction are usually small and sometimes negligible parts of the energy of the total system. Thus the parts that we ignore have to be regarded as potentially major perturbations, which may often seriously interfere with the analysis since they cannot be varied in a systematic manner.

In the present communication we describe our observations on O···C=O interactions and compare them with the data on N···C=O interactions.

The similarities and differences between the two types of interaction portray similarities and differences in the behaviour of O and N as nucleophiles and lead us to conclude that the reaction paths are similar for these two nucleophiles. The data also allow us to draw some tentative conclusions about some features of the potential energy surface, especially in the region of the tetrahedral product of the addition reaction, which

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may have some relevance to the enzymatic hydrolysis of esters and amides.

In the subsequent analysis the proton displacements in the sequence I → II → III will be neglected. But it is quite clear that the course of any actual nucleophilic addition or elimination must also be influenced by the local availability of proton donors and acceptors (acid and base hydrolysis) as well as by solvent effects.

Experimental data

A scan of the crystallographic literature revealed many examples of intra- and intermolecular O· · ·C=O interactions, of which several have already been commented on and discussed in terms of donor–acceptor or dipole–dipole interactions (Bolton, 1963, 1964, 1965; Fedeli & Dunitz, 1968; Bent, 1968). The examples form quite a heterogeneous collection. Intramolecular interactions occur in diketones, dicarboxylic acids, diesters, nitroaldehydes and ketones, and in various polyfunctional molecules. Most of the intermolecular ex-

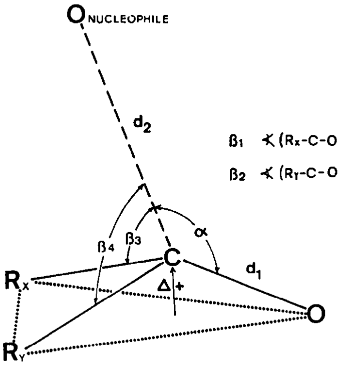


Fig. 1. Definition of symbols.

Table 1. *Intermolecular, long distance* O· · ·C=O *interactions*

For definition of symbols see Fig. 1.

Compound	R_X	R_Y	α	β_1	β_2	β_3	β_4	γ	σ^b	d_1	d_2	Δ^c	σ^b	Ref.
2,6-Dichloro-p-benzoquinone	C	C	95.1°	122.9°	121.9°	84.7°	92.0°	115.1°	0.4°	1.206 Å	2.839 Å	0.017 Å	0.007 Å	1
	d		80.0	122.9	121.9	94.1	94.5	115.4	0.4	1.206	3.094	-0.017	0.007	
	C	C	80.1	121.3	121.2	94.6	95.9	117.5	0.4	1.210	3.088	0.002	0.007	
Chloranil (at 110°K)	C	C	99.5	121.1	121.5	84.3	87.3	117.4	0.1	1.211	2.770	0.011	0.002	2
Chloranil (room temp.)	C	C	99.4	122.5	120.4	83.9	87.0	117.1	0.7	1.19	2.85	0.005	0.01	3
Chloro-p-benzoquinone	C	C	97.7	120.9	120.4	91.3	82.0	118.7	0.5	1.221	3.135	0.009	0.005	4
O-Benzoquinone	C	C	99.1	123.0	119.6	92.5	78.1	117.4	0.1	1.216	3.028	0.003	0.002	5
	d		99.6	123.0	119.6	96.2	72.8	117.4	0.1	1.216	3.102	-0.003	0.002	
2,5-Dichloro-p-benzoquinone	C	C	90.6	121.2	121.8	100.2	78.9	117.1	0.3	1.217	3.090	-0.003	0.004	6
2,3-Dichloro-p-benzoquinone	C	C	84.7	121.3	121.6	78.5	106.3	117.1	0.5	1.217	3.175	-0.006	0.005	7
Gibberillic acid deriv.	C	C	95.8	127.6	118.7	86.3	94.0	113.3	1.0	1.30	2.78	0.05	0.04	8
D-Galactone-γ-lactone	O	C	107.9	121.7	128.5	81.2	84.4	109.5	0.4	1.199	3.222	0.046	0.006	9
Barbituric acid	N	C	106.2	122.3	121.5	83.5	82.7	116.1	0.7	1.19	2.90	0.02	0.01	10
Succinimide	N	C	112.2	123.8	128.4	77.2	79.4	107.7	0.6	1.21	3.16	0.02	0.01	11
	N	C	107.7	123.9	127.2	82.8	78.7	108.8	0.6	1.24	3.27	0.01	0.01	
	d		110.3	123.9	127.2	77.1	77.9	108.8	0.6	1.24	3.16	-0.01	0.01	
Parabanic acid	N	N	89.8	126.1	126.0	92.1	90.4	107.8	0.3	1.212	3.026	0.016	0.006	12
	d		70.5	126.1	126.0	84.0	117.6	107.8	0.3	1.212	3.264	-0.016	0.006	
	N	C	90.9	129.5	125.7	92.0	87.9	104.7	0.3	1.216	2.767	0.008	0.006	
	d		82.0	129.5	125.7	107.0	81.3	104.7	0.3	1.216	3.004	-0.008	0.006	
	N	C	90.3	129.0	126.3	109.7	69.9	104.6	0.3	1.209	3.161	0.006	0.006	
	d		104.5	129.0	126.3	97.5	62.5	104.6	0.3	1.209	3.118	-0.006	0.006	
Urea-Parabanic acid complex	N	C	104.3	127.4	126.2	87.6	77.0	106.3	0.6	1.21	2.84	0.01	0.01	13
Maleic anhydride	O	C	101.1	120.2	132.3	79.9	86.7	107.5	0.3	1.195	2.995	0.002	0.005	14
	O	C	95.3	121.3	130.9	90.1	83.9	107.8	0.3	1.183	3.140	-0.001	0.005	
Succinic anhydride	O	C	106.9	119.2	130.4	80.5	80.4	110.4	0.7	1.19	3.02	0.00	0.01	15
	O	C	102.9	119.6	130.3	79.3	85.6	110.2	0.7	1.19	3.10	0.00	0.01	
	d		117.1	119.6	130.3	71.8	77.4	110.2	0.7	1.19	3.24	0.00	0.01	

(*a*) In all cases a keto-oxygen acts as nucleophile. (*b*) Average e.s.d.'s of bond angles and interatomic distances. (*c*) $\Delta > O$: displacement of electrophilic carbon towards nucleophile; $\Delta < O$: away from nucleophile. (*d*) This contact and the previous one are on opposite sides of the same electrophilic carbon.

(1) Rees (1970*b*). (2) Van Weperen & Visser (1972). (3) Chu, Jeffrey & Sakurai (1962). (4) Rees (1970*a*). (5) Macdonald & Trotter (1973). (6), (7) Rees (1970*c*). (8) Maier, Kapechi & Paul (1971). (9) Jeffrey, Rosenstein & Vlasse (1967). (10) Bolton (1963). (11) Mason (1961). (12) Davies & Blum (1955). (13) Colman & Medlin (1970). (14) Marsh, Ubell & Wilcox (1962). (15) Ehrenberg (1965).

amples involve interactions between pairs of carbonyl groups. Since we also require structural data for the tetrahedral product of the addition reaction we have also assembled information on geminal diols, ketals, hemiketals, acetals and hemiacetals, and orthoesters. We do not claim that our examples are comprehensive; indeed it is likely that a thorough search of the literature would reveal at least as many additional examples as those listed here – but we believe that our list is representative.

Table 2. *Intramolecular, long distance* O···C=O *interactions*

For definition of symbols see Fig. 1.[(a)]

	Nucleophile	Electrophile	α	β_1	β_2	β_3	β_4	γ	σ^b	d_1	d_2	Δ^c	σ^b	Ref
Bromoanhydrotetrodoic lactone hydrobromide	$-\underline{\underline{O}}-H$	lactone^d	122°	120°	126°	93°	64°	112°	2°	1.22Å	2.91Å	0.10Å	0.02Å	1
4-Bromo-2'-nitro chalcone	$-N\underline{\underline{O}}_2$	ketone	123	114	127	78	81	118	2	1.23	2.64	0.10	0.03	2
3-Chloro-2'-nitro chalcone	$-N\underline{\underline{O}}_2$	ketone	105.0	119.3	121.6	80.0	92.3	118.5	0.5	1.190	2.585	0.062	0.007	2
Cis-1,2-Dibenzoyl ethylene	$\rangle C=\underline{\underline{O}}$	ketone	103.4	122.5	119.1	92.3	79.0	118.1	0.8	1.210	2.671	0.043	0.013	3
Cis-1,2-Di-p-chlorobenzoyl ethylene	$\rangle C=\underline{\underline{O}}$	ketone	107	122	119	92	75	119	1	1.22	2.85	0.03	0.01	3
6-Ketononanolide	$-\underline{\underline{O}}-$	ketone	110.1	120.1	120.4	83.5	79.9	119.4	0.3	1.210	2.827	0.028	0.005	4
1,3,5,7-Tetraoxa-9-aza cyclodecanon	$-\underline{\underline{O}}-$	e	107.1	124.8	123.2	87.4	76.8	111.9	-	1.213	2.796	0.025	-	5
o-Nitrobenzaldehyd	$-N\underline{\underline{O}}_2$	aldehyde^d	134.2	122.2	122.4	77.1	61.5	115.2	0.6	1.20	2.70	0.02	0.01	6
Tetracyclododecatriene derivative	$CH_3-\underline{\underline{O}}-COR$	ester^d	77.2	125.8	123.8	73.7	125.5	110.3	0.4	1.211	2.924	0.019	0.008	7
	$CH_3-\underline{\underline{O}}-COR$	ester^d	87.4	122.5	124.4	70.1	113.9	113.1	0.4	1.198	2.758	0.011	0.008	
Oxindoline derivative	$\rangle C=\underline{\underline{O}}$	ketone	108.5	125.9	122.1	73.9	106.5	112.0	0.5	1.20	3.04	0.01	0.01	8
o-Nitrobenzoic acid	$-N\underline{\underline{O}}_2$	carboxylic acid^d	68.1	121.4	121.1	70.0	138.3	117.5	0.6	1.22	3.09	0.01	0.01	9
Labdanolic acid derivative	$\rangle C=\underline{\underline{O}}$	ester^d	82	131	120	127	59	110	1	1.19	3.08	0.01	0.01	10
Ammonium 2,3-Diisopropyl-maleamate	$-\underline{\underline{O}}-COR$	amide^d	106.3	127.7	118.3	86.4	76.8	119.1	0.4	1.241	3.02	-0.001	0.006	11
Stemonamine	$-\underline{\underline{O}}-H$	ketone	116	129	122	90	55	109	1	1.21	2.91	-0.01	0.01	12

(*a*) Electrophilic and nucleophilic centres are separated by at least three atoms. (*b*) See Table 1. (*c*) See Table 1. (*d*) $R_x = C$; $R_y = H$ N or O. (*e*) $R_x = N$; $R_y = O$.

(1) Furusaki, Tomiie & Nitta (1970*a*). (2) Jungk & Schmidt (1970). (3) Rabinovich, Schmidt & Shaked (1970). (4) Fedeli & Dunitz (1968). (5) Kobelt & Paulus (1973). (6) Coppens (1964). (7) Declerq, Germain & Henke (1973). (8) Bergman, Abrahamson & Dahlén (1971). (9) Sakore, Tavale & Pant (1967). (10) Bjåmer, Ferguson & Melville (1968). (11) Roberts & Kennard (1973).

Table 3. *Intramolecular, long distance* O···C=O *interactions: carboxylic acids*

For definition of symbols see Fig. 1.

Compound	d(C=O) Nucleophile	α	β_1	β_2	β_3^a	β_4^a	γ	σ^b	d_1	d_2	Δ^c	σ^b	Ref.
Cyclohexane-1,2-trans-dicarboxylic acid	1.249 Å 1.259	103.2° 87.8	123.9° 122.0	118.5° 119.1	104.0° 126.7	64.2° 56.6	117.4° 118.8	0.5° 0.5	1.255 Å 1.249	2.962 Å 3.305	0.031 Å 0.015	0.008 Å 0.008	1
Norborna-5-ene-2,3-endo-dicarboxylic acid	1.19 1.30	110.8 72.8	121.9 122.2	126.7 125.4	81.5 128.7	80.0 73.8	114.2 112.3	0.5 0.5	1.22 1.19	2.94 3.17	0.03 0.00	0.02 0.02	2
Cyclooctane-1,2-cis-dicarboxylic acid	1.221 1.313	107.9 87.3	121.9 122.4	123.3 122.9	93.1 119.2	71.1 64.8	114.7 114.6	0.4 0.4	1.231 1.221	2.838 3.006	0.027 0.004	0.005 0.005	3
Cyclohexane-1,2-cis-dicarboxylic acid	1.213 1.233	92.6 79.9	123.6 123.3	120.7 124.1	108.8 130.7	71.1 61.8	115.6 112.6	0.3 0.3	1.233 1.213	2.889 3.172	0.027 -0.011	0.004 0.004	4
Cyclooctane-1,2-trans-dicarboxylic acid	1.225 1.243	91.2 87.0	123.0 122.6	121.1 123.0	108.6 115.0	52.9 69.6	115.9 114.4	0.4 0.4	1.243 1.225	2.849 2.949	0.022 0.007	0.004 0.004	5
Cyclobutane-1,2-cis-dicarboxylic acid	1.234 1.246	80.8 80.0	123.2 123.4	120.6 120.6	120.3 118.8	71.5 74.5	116.2 115.9	0.2 0.2	1.248 1.234	2.996 3.017	0.021 0.014	0.003 0.003	6
Benzene-1,2,4,5-tetracarboxylic acid	1.213	91.8	124.2	121.6	100.0	80.2	114.1	0.4	1.208	2.672	0.019	0.006	7
Cyclopentane-1,2-trans dicarboxylic acid	1.244 1.262	109.2 107.3	123.1 123.2	119.7 118.3	108.6 109.5	49.7 50.6	117.1 118.5	0.2 0.2	1.244 1.252	3.596 3.579	0.018 0.016	0.009 0.009	8
Benzene-1,2,3-tricarboxylic acid^d	1.215 1.206	94.7 93.9	124.7 124.7	122.4 122.4	91.3 92.4	83.8 82.9	112.9 112.9	0.5 0.5	1.208 1.208	2.599 2.627	0.002 -0.002	0.005 0.005	9

(*a*) β_3 is the angle O···C–OH, β_4 is the angle O···C–C. (*b*) – (*d*) See Table 1.

(1) Benedetti, Corradini & Pedone (1969). (2) Avitabile, Ganis & Nemiroff (1973). (3) Bürgi & Dunitz (1968). (4) Benedetti, Pedone & Allegra (1970). (5) Dobler, Dunitz & Mugnoli (1966). (6) van der Helm, Nan Hsu & Sims (1972). (7) Takusagawa, Hirotsu & Shimada (1971). (8) Benedetti, Corradini & Pedone (1972). (9) Fornies-Marquina, Courseille, Busetta & Hospital (1972).

Table 4. *Tetrahedral carbon with two oxygen substituents*[(a)]

For definition of symbols see Fig. 1.

Compound	α	β_1	β_2	β_3	β_4	γ	σ^b	d_1	d_2	σ^b	$\Delta\beta^c$	Δd^d	Ref.
Ryanodol-p-bromo benzylether	109°	113°	114°	100°	106°	114°	1.2	1.33 Å	1.46 Å	0.02 Å	21°	0.13 Å	1
α-D-Glucosyl-β-D-fructoside derivative	110.8	124.1	110.7	102.0	105.4	102.7	0.6	1.37	1.48	0.01	27.4	0.11	2
Boromycinone	112	110	111	105	108	111	0.9	1.39	1.45	0.02	8	0.06	3
	107	110	112	107	106	115	1.1	1.41	1.47	0.02	9	0.06	
Ninhydrin	113.5	111.1	116.4	108.3	104.1	102.4	0.4	1.360	1.414	0.006	15.1	0.054	4
α-D-Glucose	111.6	109.4	112.0	110.1	104.8	109.0	0.2	1.389	1.425	0.005	6.5	0.036	5
α-D-Glucoseptano-	106.3	111.0	110.5	107.3	107.9	113.5	0.7	1.409	1.442	0.011	6.3	0.033	6
side derivative	106.5	111.0	109.6	106.0	109.5	113.9	0.7	1.410	1.436	0.011	5.1	0.026	
1-Thioglucoseptanoside derivative	105	108	112	109	110	113	1.0	1.44	1.47	0.02	1	0.03	7
	103	108	109	110	108	118	1.0	1.46	1.46	0.02	1	0.00	
Monensin	110.8	109.0	110.7	108.7	104.6	113.0	0.7	1.41	1.44	0.01	6.4	0.03	8
	109.9	108.1	105.2	109.6	107.0	117.0	0.7	1.42	1.45	0.01	-3.3	0.03	
Octahydroxycyclobutane	112.7	113.0	115.7	111.3	112.5	89.8	0.3	1.372	1.400	0.005	4.9	0.028	9
	110.8	115.1	111.7	114.6	113.0	90.2	0.3	1.380	1.389	0.005	-0.8	0.009	
α-D-Altropyranoside derivative	104.0	110.8	109.7	109.3	108.4	114.3	0.5	1.422	1.448	0.010	2.8	0.026	10
Alloxan tetrahydrate	114.8	109.0	109.0	105.2	105.2	113.7	0.3	1.384	1.407	0.005	7.6	0.023	11
Sucrose	110.0	105.2	107.2	108.4	109.9	115.0	0.1	1.408	1.429	0.001	-5.9	0.021	12
	110.5	105.2	110.9	110.2	110.3	109.6	0.1	1.411	1.422	0.001	-4.4	0.011	
Sialic acid	108.9	112.3	106.9	109.9	106.0	112.6	0.4	1.400	1.420	0.006	3.3	0.020	13
2,6-Anhydro-β-D-fructofuranose	104.4	102.3	114.3	109.2	110.5	115.4	0.3	1.411	1.430	0.003	-3.1	0.019	14
	104.4	101.9	112.7	108.2	112.3	116.3	0.3	1.425	1.427	0.003	-5.9	0.002	
Vitamin D derivative	105.5	110.7	108.5	110.9	109.5	111.5	0.4	1.407	1.422	0.006	-1.2	0.015	15
	104.5	112.5	109.7	106.4	109.9	113.4	0.4	1.415	1.429	0.006	5.9	0.014	
β-D-Fructopyranoside derivative	111.8	109.8	104.7	107.8	107.3	115.4	0.4	1.413	1.426	0.004	-0.6	0.013	16
	105.3	108.7	109.9	109.7	109.2	113.6	0.4	1.43	1.441	0.004	-0.3	0.008	
	105.4	108.5	109.1	109.2	110.9	113.3	0.4	1.428	1.434	0.004	-2.5	0.006	
Chloralhydrate	112.1	108.7	111.3	111.7	106.5	106.5	0.1	1.386	1.397	0.002	1.8	0.011	17
Tricyclododecane derivative	110.6	103.6	112.7	112.3	103.8	114.0	0.3	1.420	1.430	0.004	0.2	0.010	18
Dimeric cyclohexanone peroxide	105.6	105.6	113.2	104.5	112.3	112.7	0.2	1.429	1.439	0.003	2.0	0.010	19
Trimeric acetone peroxide	112.6	103.0	113.3	112.5	102.6	113.3	0.4	1.417	1.426	0.005	1.2	0.009	20
	111.8	112.1	103.3	102.7	112.1	115.2	0.4	1.422	1.429	0.005	0.6	0.007	
	112.5	103.1	112.9	112.2	103.4	113.0	0.4	1.418	1.422	0.005	0.4	0.004	
Dimeric cyclooctanone peroxide	107.1	112.7	103.7	110.7	103.6	118.0	0.1	1.436	1.442	0.002	2.1	0.006	21
Alloxan hydrate	113.2	111.3	107.2	103.1	108.2	113.9	0.3	1.389	1.394	0.005	7.2	0.005	22
α- -Sorbose	110.2	107.2	111.1	109.5	106.9	111.9	0.3	1.415	1.420	0.005	1.9	0.005	23
Dimeric cycloheptanone peroxide	107.8	112.9	102.9	111.4	103.8	117.2	0.3	1.434	1.437	0.004	0.6	0.003	24

(*a*) See (IV), (V), (VI). (*b*) See Table 1. (*c*) $\Delta d = d_2 - d_1$. (*d*) $\Delta\beta = \beta_1 + \beta_2 - \beta_3 - \beta_4$.

(1) Srivastava & Przybylska (1970). (2) Isaacs & Kennard (1972). (3) Marsh, Dunitz & White (1974). (4) Medrud (1969). (5) Brown & Levy (1965). (6) Jackobs, Reno & Sundaralingam (1973). (7) Beale, Stephenson & Stevens (1972). (8) Lutz, Winkler & Dunitz (1971). (9) Bock (1968). (10) Hung-Yin Lin, Sundaralingam & Jackob (1973). (11) Mootz & Jeffrey (1965). (12) Brown & Levy (1973*a*). (13) Flippen (1973). (14) Dreissig & Luger (1973). (15) Knobler, Romers, Braun, & Hornstra (1972). (16) Takagi, Shiono & Rosenstein (1973). (17) Brown & Levy (1973*b*). (18) Baker & Pauling (1972). (19) Groth (1967*a*). (20) Groth (1969). (21) Groth (1967*c*). (22) Singh (1965). (23) Kim & Rosenstein (1967). (24) Groth (1967*b*).

In order to find structural relationships the positions of all four atoms attached to or interacting with the central carbon atom must be known with reasonable accuracy. Many examples where one of these atoms is hydrogen had to be discarded, either because the H positions were not determined in the course of the structure analysis or because they were not known with sufficient accuracy for our purposes. A few structures containing heavy atoms were also omitted because of large uncertainties in the C and O positions. Otherwise we have included in Tables 1-5 all the examples we have examined.

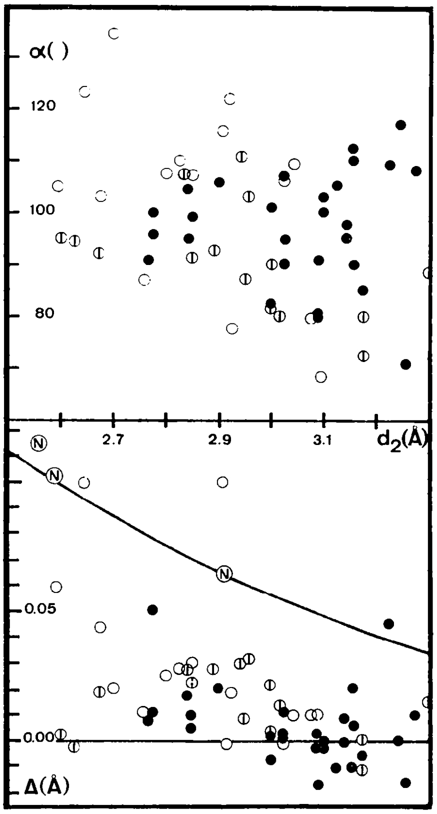


Fig. 2. Scatter plots of O···C=O distance d_2 against O···C=O angle α (above) and against displacement Δ of carbon from the $R_x R_y O$ plane (below). Data from Table 1 (●), Table 2 (o) and Table 3(⊙). The corresponding curve d_2 (N···CO) against Δ is also shown Ⓝ (Bürgi, Dunitz & Shefter, 1973).

The relative positions of five atoms, R_1, R_2, C, O, and O (nucleophile), can be defined in terms of nine independent geometric parameters, which are conveniently taken as the four distances from the central C atom plus any five of the six angles around this atom. The relevant structural parameters are illustrated in Fig. 1 and listed in Tables 1-5. In all cases we have recalculated the parameters from crystal coordinates given in the references. Where slight discrepancies occurred between our calculated parameters and the published ones we have used our values for self-consistency.

Long distance O··· C=O interactions

When a nucleophilic O atom is less than about 3 Å away from an electrophilic C atom, the latter is displaced from the plane defined by R_1, R_2 and the carbonyl O atom towards the nucleophile (Tables 1-3, Fig. 2). Some of these displacements Δ from planarity are mentioned in published descriptions of individual structures but they were rarely regarded as significant and never discussed in terms of the nucleophilicity of the crystal environment of the carbonyl carbon atom.

The plot of O···C distance d_2 *versus* Δ (Fig. 2) shows considerable scatter, but there is a definite tendency for the displacement Δ to increase with decreasing d_2. For comparison, a portion of the displacement curve for N···C=O interactions is also shown in Fig. 2. In spite of the scatter in the individual O···C=O displacement points there is no doubt that, at least for nucleophile···carbon distances greater than 2·5 Å, a mean O···C=O displacement curve would lie well below the N···C=O curve, which follows the function $d = 1{\cdot}701 \log \Delta + 0{\cdot}867$ Å. Indeed, for the same nucleophile···carbon distance the O···C=O displacement is only about a third of that given by the above function, indicating that alcoholic or keto oxygens are, in general, weaker nucleophiles than amine nitrogens.

Several factors, besides experimental inaccuracy in the atomic positions, contribute to the scatter in Fig. 2. In some cases the carbonyl C is engaged in two O···C=O interactions, one on each side of the plane, so that the net displacement Δ may be regarded as the resultant of two displacements in opposite directions. Also, as mentioned, the nucleophilic O atoms are very heterogeneous (carbonyl, ether, carboxylate, nitro

Table 5. *Ortho-acid derivatives*

Compound	α_1^c	α_2^c	α_3^c	β_1^c	β_2^c	β_3^c	σ^b	d_1	d_2	d_3	σ^b	S_{2b}^d	S_{6b}^d	Ref.
Carbohydrate orthoester	110.9°	110.7°	113.8°	105.3°	110.3°	105.4°	0.4°	1.420 Å	1.411 Å	1.404 Å	0.007 Å	6°	-0.023 Å	1
Tetrodotoxin hydrobromide[a]	110	110	114	105	109	109	~ 2	1.44	1.46	1.37	0.03	8°	-0.16	2
Diacetylanhydrotetrodotoxin hydroiodide	111	107	115	108	110	108	~ 2	1.44	1.44	1.34	0.03	12°	-0.20	3

(*a*) Average from two molecules in the asymmetric unit. (*b*) See Table 1. (*c*) OCC angles: α_i; OCO angles: β_i. (*d*) Symmetry coordinates chosen on the basis of Herzberg (1960) $S_{2b} = 2\alpha_3 - \alpha_2 - \alpha_1$; $S_{6b} = 2r_3 - r_2 - r_1$ (V).
(1) Heitmann & Richards (1973). (2) Furusaki, Tomiie & Nitta (1970*b*). (3) Tamura, Amakasu, Sasada & Tsuda (1966).

groups, *etc.*). Thirdly, the strength of the interaction may be expected to depend on the mutual orientation of the groups containing donor O and electrophilic C. For intermolecular O···C=O interactions the substituents on the electrophilic and nucleophilic groups may interfere and prevent too close an approach. For intramolecular interactions geometric constraints due to the relative inflexibility of bond lengths and bond angles along the chain(s) connecting donor and acceptor may prevent an optimal interaction.

In spite of these limitations the available data make it possible to give an idealized geometric description of long distance O···C=O interactions. The main features may be summarized as follows: (1) we find no intermolecular O···C=O distance smaller than 2·77 Å, whereas intramolecular O···C=O distances as short as 2·58 Å are observed; (2) although the distribution of O···C=O angles is different for the intermolecular and intramolecular cases and also seems to depend on the class of compound involved (Fig. 3), there is a clear tendency for these angles to cluster between 100 and 110°; (3) the nucleophile tends to be situated approximately in the plane bisecting the angle R_1CR_2, as may be seen from the relationships $\beta_1 \sim \beta_2$ and $\beta_3 \sim \beta_4$.

In the N···C=O case the nucleophile was found to approach the carbonyl at a fairly constant N···C=O angle of 107 ± 5°. The same constancy is not found in our O···C=O examples, where the angle varies from less than 90° to more than 130°. This variation may be due to some extent to the weaker strength of the O···C=O interaction, which makes the geometry more susceptible to the effects of external perturbations, but it is also connected with the very different geometric constraints that are operative in many of our intramolecular cases. For example, in the 1,2-dicarboxylic acids, where O···C=O interactions are clearly expressed by the small but significant deviations of the carboxyl groups from planarity, geometric constraints make it virtually impossible for the carbonyl O of one carboxyl group to approach the C atom of the other carboxyl group at a favourable angle.

As seen from Tables 1 and 3, the oxygen atom of one carbonyl group often acts as nucleophile with the carbon of a second carbonyl group as electrophile. The examples fall into two main groups. In one group the planes of the two R_1R_2C=O systems are either roughly parallel or perpendicular to each other, the angles C=O···C lie in the range 100 to 130°, and the O···C distances tend to be on the long side. All the short O···C distances occur in the second group where the two planes are roughly perpendicular and the C=O···C angles are in the range 150 to 180°.

It seems fairly clear that pyramidalization of the carbonyl group (considered in isolation) will increase the potential energy, whereas the nucleophile–carbon interaction will lower it. For X···C distances between 2·5 and 3 Å, Δ(N···C=O) is about three times larger than Δ(O···C=O), corresponding to an energy cost that is about ten times larger, assuming a quadratic dependence on Δ. This suggests that the N···C interaction energy is also about ten times greater than the O···C interaction energy at the same distance, in agreement with the supposed 'better' nucleophilicity of N.

The order of magnitude of the pyramidalization energy (and hence a lower limit to the interaction energy) can be estimated from the out-of-plane bending force constant of a carbonyl group, which is roughly 50 kcal $\text{mole}^{-1}\text{rad}^{-2}$ (in terms of the out-of-plane bending coordinate χ, the dihedral angle between the planes RCR′ and OCR′). After making the appropriate transformations, this leads to a pyramidalization energy of about 200 Δ^2 kcal $\text{mole}^{-1}\text{Å}^{-2}$, equal to 0·5 kcal mole^{-1} for $\Delta = 0{\cdot}05$ Å.

Fig. 3 hints that the O···C=O interaction energy (as measured by the degree of pyramidalization) also depends on the O···C=O angle. The interaction appears to be somewhat stronger when this angle is around 110° but the clarity of the picture is obscured by numerous other factors, in particular, the intrinsic differences in nucleophilicity between the various kinds of O atoms that occur in our list. The O atoms of nitro groups, for example, appear to interact strongly with neighbouring carbonyls, judging from the fact that the shortest O···C distances (and the largest Δ's) involve nitro groups.

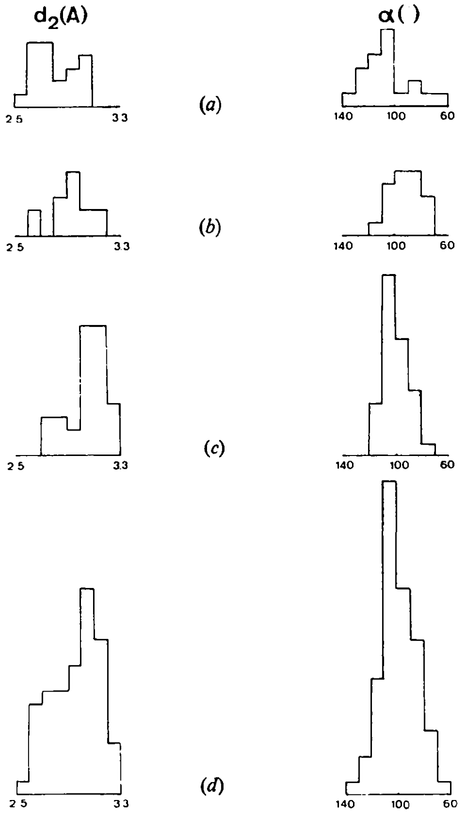


Fig. 3. Distribution of d_2 and α: (*a*) data from Table 1, (*b*) data from Table 2, (*c*) data from Table 3, (*d*) all data.

Whereas our six sample points in the N···C=O case cover the whole range of N···C distance from about 1·5 Å (covalent bonding) to about 3 Å, there is a large region extending from just over 1·5 Å to about 2·5 Å where we have no O···C=O points. It is possible that this lacuna is due to an unfortunate choice of examples – after all, we have relied on the more or less unsystematic provision of data and have no example of a transannular O···C=O interaction in an eight-membered ring comparable to the N···C=O interaction in clivorine (d=1·993 Å! Birnbaum, 1972). However, there is also the possibility that this gap occurs because O···C distances in the intermediate range 1·5–2·5 Å would correspond to unfavourable interaction energies. We are currently carrying out crystal structure analyses of molecules, *e.g.* 1-methoxy-8-carbomethoxynaphthalene, in which the O···C distance is subject to geometric constraints that force it to lie in this intermediate region.

The tetrahedral subunit

Tetrahedral subunits with two O atoms attached to the same C atom represent an extreme case of O···C=O interaction where the addition reaction has proceeded to completion. Again we have a large and heterogeneous collection of examples of several types (diols, ketals, hemiketals, acetals, hemiacetals) which introduces unpredictable sources of scatter into any possible correlation of the data.

The only interesting trend we have been able to find is between the quantities $\Delta\beta=\beta_1+\beta_2-\beta_3-\beta_4$ and $\Delta d=d_2-d_1$ (see Fig. 1 and Table 4). The scatter plot of $\Delta\beta$ against Δd (Fig. 4) shows a clear tendency for large positive values of Δd to be associated with large positive values of $\Delta\beta$. The equation obtained by linear regression (assuming an intercept of zero) is

$$\Delta\beta(°)=173\Delta d\,(\text{Å}). \tag{1}$$

The corresponding correlation coefficient r equals 0·84. The differences Δd and $\Delta\beta$ are proportional to the symmetry displacement coordinate S_9 and S_{10} (Dennen, 1968) for a tetrahedron of C_{2v} symmetry

$$S_9=(d_2-d_1)/\sqrt{2} \tag{2}$$

$$S_{10}=(\beta_1+\beta_2-\beta_3-\beta_4)/2. \tag{3}$$

Both deformations belong to the same representation B_1 of the C_{2v} point group and hence can mix according to the expression

$$2V=k_9S_9^2+k_{10}S_{10}^2+2k_{9,10}S_9S_{10} \tag{4}$$

for the relevant part of the potential energy expression. If we assume that the sample points tend to accumulate in regions of the parameter space of the subsystem which have low potential energy we can estimate the directions of the principal axes of the quadratic form (4). From the data in Table 2 the potential energy valley is inclined at an angle α of approximately 25° to the S_{10} axis, from which the ratio of the interaction constant $k_{9,10}$ to the difference of the diagonal force constants k_9 and k_{10} can be estimated from the relationship

$$\tan 2\alpha=\frac{2k_{9,10}}{k_{10}-k_9}\,. \tag{5}$$

The three corresponding force constants of the methylene dihalides CH_2F_2, CH_2Cl_2, CH_2Br_2, CH_2I_2 have been determined from spectroscopy (Dennen,

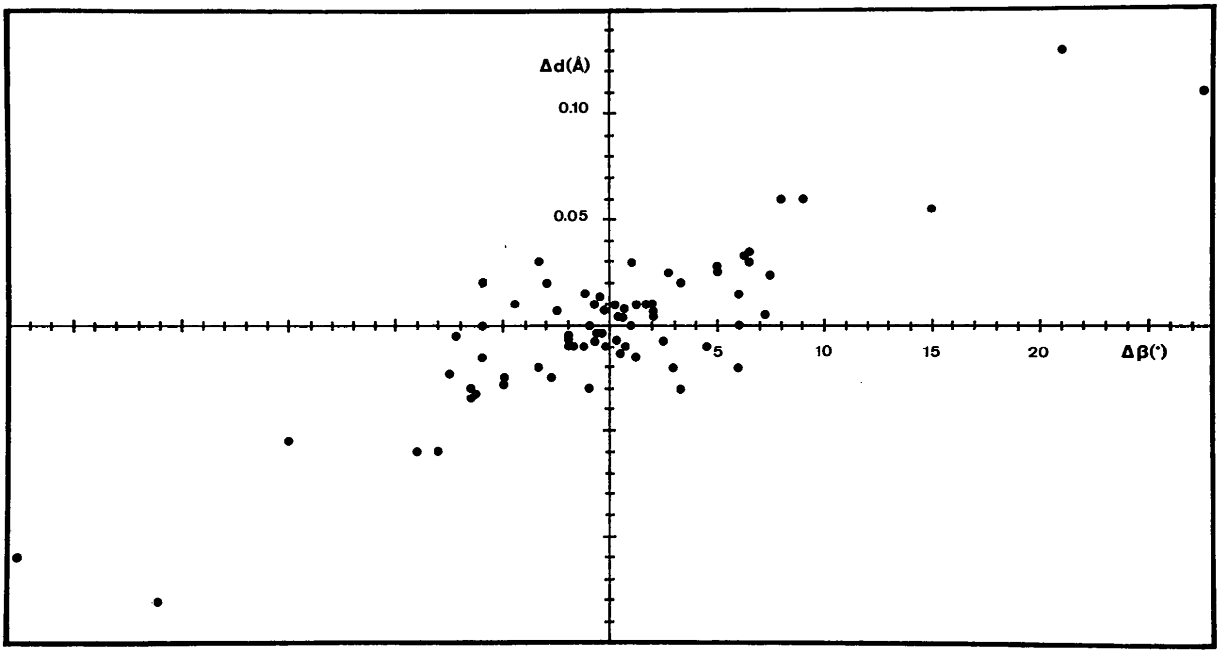
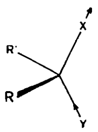


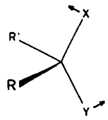
Fig. 4. Scatter-plot of Δd against $\Delta\beta$ (data from Table 4, definition of variables in the text).

1969). The quantity tan 2α is found to have the same sign as deduced for our tetrahedral subunit implying that the interaction constants $k_{9,10}$ also have the same sign.

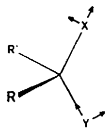
Although the quadratic force field assumed in the above discussion is only valid for small displacements, the results strongly suggest that, in the minimum energy path for decomposition of a tetrahedral intermediate, the leaving group X does not simply depart along the line of the C–X bond. Instead, as the bond C–Y shortens and the bond C–X weakens (IV) the coupling between the antisymmetric bend (V) and stretch (IV) coordinates comes into operation. The shortening C–Y bond moves towards the RCR′ plane and the direction of departure of the leaving group X is continuously adjusted to retain an XCY angle of about 110° (VI):



(IV)



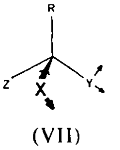
(V)



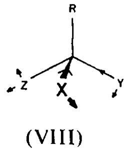
(VI)

This constancy of the angle XCY was found over even wider ranges of d_1 and d_2 for N–C–O interactions (Bürgi, Dunitz & Shefter, 1973) and was interpreted in terms of a preferred direction of approach of the nucleophile to the carbonyl function. Of course, the N···CO data could also have been discussed in terms of the decomposition of the tetrahedral RR′CNO intermediate leading to conclusions analogous to those described above.

By analogy with the RR′CXY case we can expect that the minimum energy path for decomposition of orthoester and amide acetal tetrahedral structures RCXYZ (with three electronegative substituents, X,Y=OR, Z=OR or NR_2), formed as intermediates in the hydrolysis of esters, lactones, lactams and amides, will also involve a coupling between bend and stretch coordinates. For C_{3v} symmetry of such an intermediate there would be two degenerate vibration modes (Herzberg, 1945) that could lead to decomposition (VII, VIII):



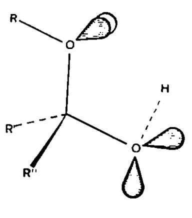
(VII)



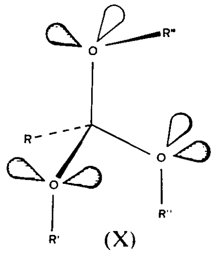
(VIII)

Unfortunately, the structural information for compounds containing these features is so sparse and inaccurate that no firm conclusions can be drawn. However, results of three recent X-ray analyses, one orthoester and two ortho-acid diesters, are compatible with the second of these vibration modes (VIII with reversed phase). One C–O bond, C–Z say, is markedly shorter than the other two C–O bonds and the angle RCZ is markedly larger than the other two angles RCX and RCY (Table 5).

So far we have avoided any theoretical discussion of the correlations that we have observed. They probably depend on a number of factors, including differences in crystal packing, substitution of the oxygen atoms, conformation around C–O bonds, hydrogen bonding, *etc*. Among these possibilities the influence of conformation has been studied in detail by non-empirical MO calculations for methylenediol, triol and tetrol (Jeffrey, Pople & Radom, 1972; Lehn, Wipff & Bürgi, 1974). These calculations have shown that the geminal C–O bond lengths depend on the torsion angles in the H–O–C–O–H system. For example, for torsion angles 60°, 180°, the calculated bond lengths are 1·396, 1·428 Å; for torsion angles +60°, +60° the calculated bond lengths are 1·421 Å. Some of the differences between the C–O bond lengths in the tetrahedral structures listed in Table 4 show the same kind of behaviour, *e.g.* in ryanodol the short C–O bond is antiplanar to an O-alkyl bond, while the long one is synclinal to an O–H bond (IX). The same argument may be extended to the orthoesters which show the short C–O distance antiperiplanar with respect to two O–R bonds and the long C–O distances antiperiplanar to lone pairs (X).



(IX)



(X)

These structural findings are complemented and reinforced by the observations of Deslongchamps and coworkers (Deslongchamps, Atlani, Fréhel & Malaval, 1972; Deslongchamps, Lebreux & Taillefer, 1973) who studied the decomposition of conformationally rigid orthoesters and amideacetals in solution. On the basis of their results these authors propose that the bond most readily broken is the one in an antiperiplanar orientation to two lone pairs, the bond that tends to be long in an equilibrium situation.

It was also pointed out – but not explained – by Jeffrey, Pople & Radom (1973) that, other things being equal, C–OH bonds tend to be shorter than corresponding C–OR bonds. In agreement with this observation all unsymmetrically substituted dioxo compounds included are in the top half of Table 4, that is, they show large differences between the two C–O bond distances, with C–OH consistently shorter than C–OR.

Whatever the origin of the differences in C–O distances (possible influences would include torsion angles, substituents, steric effects, hydrogen bonding and crystal packing) there appears to be a distinct correlation of these differences with the R–C–O angles. The longer bond tends to be associated with smaller RCO angles, the shorter bond with larger ones, *i.e.* as the C–O bond becomes shorter it tends to lie closer to the RCR′ plane.

Outlook

Many of our arguments depend on displacements from planarity (Table 1–3) and differences in bond lengths and angles (Tables 4, 5), which, taken individually, are not significant in a statistical sense. Our justification is that from the evidence taken together trends can be discerned. These trends turn out to furnish a structural basis for the discussion of chemical reactivity. Indeed, for molecules to come into reaction with each other they have to approach each other, and the details of how they approach each other may be relevant to their mutual reactivity. This point of view was stated 50 years ago by Pfeiffer (1922). 'Da die chemischen Kräfte nur in Entfernung von atomaren und molekularen Dimensionen wirken, so folgt ohne weiteres, dass zwei Moleküle, die miteinander in Reaktion treten, sich zunächst einander anlagern, worauf dann in der so entstandenen Molekülverbindung ... intramolekular die eigentliche Reaktion einsetzt.'

Solid-state organic chemistry (Cohen & Schmidt, 1964; Cohen & Green, 1973; Paul & Curtin, 1973) depends on detailed knowledge of specific intermolecular interactions to predict crystal packing and to realize suitable arrangements of reactive centres in the solid state. The concepts presented here may be useful in striving towards this goal and in discussing some aspects of solid-state reactions.

An example is provided by the thermal rearrangements of phenylazotribenzoylmethane (XI) in solution and in the solid state (Fig. 6) which have been extensively studied by Curtin and coworkers (Curtin & Miller, 1967; Curtin, Byrn & Pendergrass, 1969; Pendergrass, Curtin & Paul, 1972). The molecule forms two products on heating; α-phenylazo-β-benzoyloxybenzolacetophenone (XII) and diphenyltriketone-*sym*-benzoylphenylhydrazone (XIII). The observed O···C=O and N···C=O interactions in compound (XI) are favourably disposed for the formation of tetrahedral intermediates, which can then break down to the respective products. The observed predominance of (XIII) over (XII) for the solid-state reaction at lower temperatures is consistent with the greater strength of the N···C=O interaction in the conformation adopted in the crystal.

Much effort goes into attempts to explain the specificity and efficiency of enzymatic reactions. Kinetic studies of low-molecular-weight model compounds have demonstrated the importance of the relative orientation of reactant and substrate (Storm &

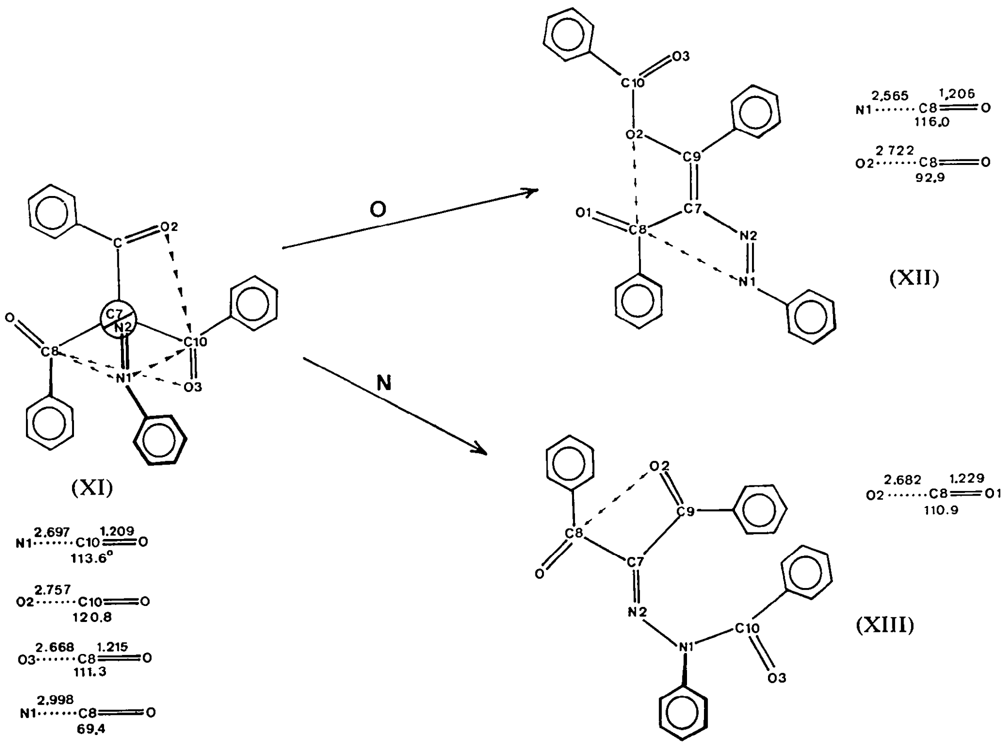


Fig. 5. Thermal rearrangements of phenylazotribenzoylmethane.

Koshland, 1972; Kirby & Lancaster, 1972) arriving at results very similar to ours (Bürgi, Dunitz & Shefter, 1973). The known structures of the active sites of the hydrolytic enzymes subtilisin BPN′ (Wright, Alden & Kraut, 1972) and α-chymotrypsin (Steitz, Henderson & Blow, 1969; Birktoft & Blow, 1972) are also compatible with the ideas presented in this paper. Along these lines, it is interesting that in the structures of the benzoyl arginine complex of subtilisin BPN′ and of the formyl-L-tryptophan complex of α-chymotrypsin, O···C=O interactions involving the inhibitor and the active serine residue appear to be present. In both cases the interaction involves the hydroxyl group of a serine (221 in subtilisin and 195 in chymotrypsin) and the carboxyl carbon of the inhibitor. We have calculated the relevant distances and angles from published coordinates. They are: for the subtilisin complex, O···C, 2·7 Å; O···C–O, 93° and 40°; for the chymotrypsin complex, O···C, 2·4 Å; O···C–O, 90° and 112°. Although these values are highly inaccurate (compared with those used in our previous discussion) they are very suggestive of the manner in which normal substrates might interact with the enzyme to give the tetrahedral intermediate involved in the hydrolysis of the peptide bond. Further support for these ideas comes from a detailed comparison (Huber, 1973) of the structures of the active sites in α-chymotrypsin (Steitz, Henderson & Blow, 1969), the complex between bovine trypsin and bovine pancreatic trypsin inhibitor (Rühlmann, Kukla, Schwager, Bartels & Huber, 1973), and in tosyl-α-chymotrypsin (Birktoft & Blow, 1972). As one goes from native enzyme to covalently bonded complex the changes in the position of serine-195-Oγ are very reminiscent of the pathway for nucleophilic addition proposed in this article.

The analysis of structural correlations allows the crystallographer to contribute more directly to problems of reaction mechanism and reaction path and hence to complement the various semi-empirical and *ab initio* quantum mechanical calculations mostly performed for isolated reactants (Dedieu & Veillard, 1972; Bürgi, Lehn & Wipff, 1974) and to establish empirical structure–energy relationships covering wide ranges of internuclear distances. Conversely the ideas presented here offer another possibility for diagnosing unusual intra- and intermolecular structural parameters. At the same time, many of the ideas need more theoretical backing, in particular, the description of the identity and properties of 'subunits' needs to be made more precise in structural and energetical terms. On the experimental side, the vast literature on structural studies and chemical reactivity offers a wide range of possible correlations to be sought. Systematic studies of chemical reactions along these lines have hardly begun, but in the light of recent advances in automatic data-collecting and structure-solving techniques such studies could well furnish the material to build a bridge between the 'statics' of crystals and the 'dynamics' of reacting chemical systems.

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