

Systematic Analysis of Structural Data as a Research Technique in Organic Chemistry

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Crystallography is the most powerful method available for studying molecular structures. It has become increasingly important in recent years with the introduction of automatic diffractometers and new methods of structure solution and refinement. There are now more than 30 000 organocarbon structures (i.e., organics, organometallics, and metal complexes) in the literature, a number that is likely to double within 5–7 years. Unfortunately, this wealth of information has not been greatly exploited; detailed discussions of individual crystal structures are commonplace, but systematic studies of large numbers of related structures are rarely undertaken.

The purpose of this Account is to illustrate how the systematic analysis of crystallographic data can be a versatile research technique in organic chemistry.¹ Examples are taken from many areas, including studies of bonding theories, conformational analysis, reaction pathways and hydrogen bonding. Many of the studies were carried out with the aid of the Cambridge Structural Database (CSD),² which is described briefly below.

Cambridge Structural Database (CSD)

CSD contains results of X-ray and neutron diffraction studies of organics, organometallics, and metal complexes. The information stored for each entry (Table I) may be divided into three categories: bibliographic information (BIB),³ chemical connectivity information (CONN), and crystallographic data (DATA). CSD is fully comprehensive from 1935 onward, and is also a depository for unpublished atomic coordinates.⁴ The database is available in 22 countries and on January 1, 1982, contained 31 631 studies of 28 978 different compounds. About 4000 new entries are added each year.

The information in CSD is searched and analyzed by a system of computer programs;² examples of program input and output are given in Figure 1. The two main search programs are BIBSER and CONNSER. BIBSER uses the bibliographic information fields italicized in Table I to locate entries on the basis of their chemical name,

After graduating from Cambridge University, Olga Kennard worked at the Cavendish Laboratory and subsequently joined the Medical Research Council in London. She returned to Cambridge in 1961, as a member of M. R. C. External Staff, to build up an X-ray crystallographic unit in the University Chemical Laboratory. The Cambridge Crystallographic Data Centre (CCDC) was established there, under her direction, in 1965. Olga Kennard's research is concerned with biological structures, particularly oligonucleotides and their interaction with drugs and proteins. She was awarded an Sc.D. (Cantab) in 1971 and the Structural Chemistry Prize of the Chemical Society in 1980.

Frank Allen obtained a Ph.D. from London University and did postdoctoral crystallographic work at the University of British Columbia. He joined the CCDC in 1970 and has been involved in many aspects of its development; he is a member of the Data Commission of the International Union of Crystallography. Current research interests involve applications of the Structural Database in physical organic chemistry.

Robin Taylor obtained a B.A. from Oxford and a Ph.D. in chemical crystallography from Cambridge University. He held postdoctoral positions in York and Pittsburgh before joining the CCDC in 1980. His research interests include the structure and energy of hydrogen-bonded systems and the application of statistical methods to crystallographic data.

Table I
Principal Information Held in the
Cambridge Structural Database (CSD)

Bibliographic (BIB)
<i>Compound name(s); qualifying phrase(s)</i> [e.g., neutron study, low-temperature study, absolute configuration determined]; <i>molecular formula, literature citation; chemical class(es)</i> [e.g., 15 = benzene nitro compounds, 51 = steroids, 58 = alkaloids, etc.]
Chemical Connectivity (CONN)
Chemical structural diagrams are coded in terms of <i>atom</i> and <i>bond properties</i> . Atom properties: atom sequence number (<i>n</i>); element symbol (<i>el</i>); no. of connected non-H atoms (<i>nca</i>); no. of terminal H atoms (<i>nh</i>); net charge (<i>ch</i>). Bond properties: pair of atom sequence numbers (<i>n = i, j</i>); bond type for bond <i>i-j</i> (<i>bt</i>); [see Figure 1, b and c].
Crystallographic Data (DATA)
Unit-cell Parameters; space group; symmetry operators; atomic coordinates; accuracy indicators [mean estimated standard deviation of C–C bonds, <i>R</i> factor]; evaluation flags [indicating: presence of disorder, presence of errors, method used for data collection, etc.]; comment text [e.g., describing any disorder, or errors in the original reference].

molecular formula, chemical class, etc. (e.g., Figure 1a). CONNSER is used to search for compounds containing specific chemical fragments. Program input consists of a coded representation of the desired fragment (e.g., the coding in Figure 1c would be used to find compounds containing the substructure shown in Figure 1b).

Output from both BIBSER and CONNSER consists of a listing of all structures in the database that satisfy the search criteria, together with the corresponding literature references (e.g., Figure 1, parts d and e). The RETRIEVE program may now be used to create a file of crystallographic data for entries located by the search. This DATA subfile can be processed by the programs PLUTO78, which produces plots and illustrations (e.g., Figure 1f), and GEOM78, which is used for geometrical analysis. GEOM78 will calculate the intra- and/or intermolecular geometries of all entries in a DATA subfile or provide systematic tabulations of selected geometrical parameters for a specific chemical fragment. Figure 1g is a tabulation of *R* factor, five independent bond lengths, and the torsion angle O(1)–C(2)–C(3)–X (X = midpoint of C(4)–C(5)) for the fragment shown

(1) This Account complements an earlier paper that was primarily concerned with the chemical interpretation of *individual* structures: Wilson, S. R.; Huffman, J. C. *J. Org. Chem.* 1980, 45, 560–566.

(2) Allen, F. H.; Bellard, S.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr. Sect. B* 1979, B35, 2331–2339 and references therein.

(3) Bibliographic information is also published annually in: "Molecular Structures and Dimensions", Kennard, O., Watson, D. G., Allen, F. H., Bellard, S., Eds.; D. Reidel: Dordrecht, The Netherlands.

(4) Journals involved in this scheme since 1977 include *Chemical Communications*, *Tetrahedron*, and *Tetrahedron Letters*.

(a) BIBSER : Sample Questions

(i) Find all steroids :

Q *CLASS '51'

Note : Chemical class 51 = steroids

(ii) Find all penicillins published between 1970 and 1980 inclusive :

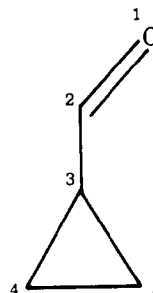
Q *COMPND 'PENICILL' and *YEAR '70-80'

Note : The string PENICILL will locate penicillin, penicillanic, penicilloic, etc.

(iii) Find all compounds for which absolute configuration has been established by X-ray methods :

Q *COMPND 'ABSOLUTE CONFIGURATION'

(b) CONNSER : Search Fragment



(c) CONNSER : Search Query
[for fragment in (b)]

```

Q Cyclopropyl-carbonyls
C
C Atom properties:
C only nca is specified :
C
AT1 O 1
AT2 C 2
AT3 C 3
AT4 C 2
AT5 C 2
C
C Bond properties :
C node numbers, bond-type,
C and Acyclic/Cyclic flag :
C
BO 1 2 2 A
BO 2 3 1 A
BO 3 4 1 C
BO 4 5 1 C
BO 3 5 1 C
END

```

(d) BIBSER : Sample Output from Question (a,i)

AAMAND 16alpha-Acetyl-3beta-methoxy-CD-cis-D-norandrostande
C21 H34 O2; Class 51
J.Meinwald,A.J.Taggi,P.A.Luhan,
A.T.McPhail
Proc.Nat.Acad.Sci.U.S.A., 71, 78, 1974

ABAXES 2alpha-Bromo-17beta-acetoxy-9-methyl-5alpha,9beta,10alpha-estran-3-one
C21 H31 Br1 O3; Class 51
J.C.A.Boeyens,J.R.Bull,J.Floor,
A.Tuinman
J.Chem.Soc.,Perkin 1, 808, 1978

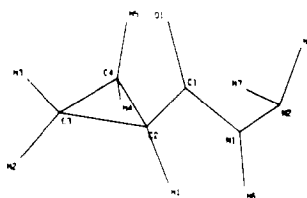
(e) CONNSER : Sample Bibliographic Listing
for Search Query (c)

CORAMA (-)-Coronamic acid N-acetate
(absolute configuration)
C8 H13 N1 O3; Class 48,20
A.Ichihara,K.Shiraishi,S.Sakamura,
A.Furusaki,N.Hashiba,T.Matsumoto
Tetrahedron Lett., 365, 1979

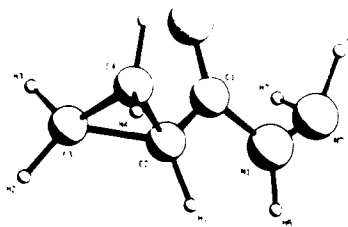
CPCOHA Cyclopropanecarbohydrazide
C4 H8 N2 O1; Class 20,9
D.B.Chesnut,R.E.Marsh
Acta Crystallogr., 11, 413, 1958

CPRPCX10 Cyclopropanecarboxamide
C4 H7 N1 O1; Class 20,1
R.E.Long,H.Maddox,K.N.Trueblood
Acta Crystallogr.,Sect.B, 25, 2083, 1969

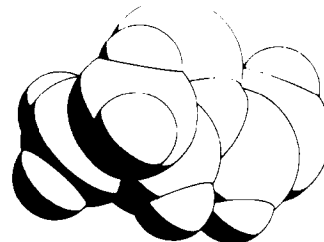
(f) PLUTO78 : Sample Plots for Cyclopropanecarbohydrazide [CPCOHA in (e)]



(i) 'stick' diagram



(ii) 'ball-and-spoke' style with shading and perspective



(iii) 'space-filling' model with shading and perspective

(g) GEOM78 : Example of Geometry Tabulation for Fragment (b)

Notes :	CSD code	*RFACT	C4-C5	C3-C4	C3-C5	C3-C2	C2-O1	TAU
Distances in Angstroms,	CORAMA	0.059	1.491	1.534	1.503	1.502	1.216	28.04
angle (TAU) in degrees.	CPCOHA	0.130	1.478	1.520	1.493	1.478	1.213	4.52
	CPRPCX10	0.087	1.467	1.485	1.501	1.484	1.238	-7.74
TAU is the torsion angle :	CPRPCX10	0.087	1.450	1.489	1.493	1.470	1.249	-4.67
O(1) - C(2) - C(3) - X(1),	DCPEDO	0.047	1.475	1.515	1.510	1.456	1.213	3.19
where X(1) is the mid-point	DMCPRC	0.085	1.477	1.521	1.510	1.456	1.246	-7.30
of the bond C(4) - C(5).	MBCPCX	0.062	1.488	1.531	1.508	1.480	1.210	30.07
STD. DEVN. is the standard	NPCPMK	0.092	1.474	1.513	1.488	1.469	1.235	8.64
deviation of each sample.	PMCPRC10	0.037	1.490	1.548	1.505	1.484	1.205	-21.17
The standard deviations of	SDPPCX	0.042	1.482	1.533	1.510	1.470	1.201	-5.47
the means are 0.004, 0.006,	MEAN		1.477	1.519	1.502	1.475	1.223	
0.003, 0.005 and 0.006.	STD. DEVN.		0.012	0.020	0.008	0.014	0.018	

Figure 1. Examples of input and output for the CSD program system.

in Figure 1b. The DATA subfile may also be processed by the user's own programs.

Systematic Analysis of Intramolecular Geometry

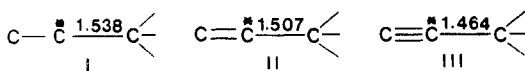
Mean Geometries. The results of early X-ray analyses were used to derive mean bond lengths,⁵ co-

valent radii, etc., which were important in the development of structural chemistry and bonding theories. As the number of structural studies increased, it became possible to determine the mean geometries of complete

(5) Sutton, L. E., Ed., "Tables of Interatomic Distances and Configuration in Molecules and Ions"; The Chemical Society: London; Special Publication 11 (1958) and 18 (1965).

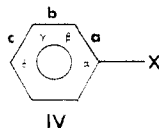
chemical residues. Thus, the average dimensions of furanose,⁶ pyranose,⁷ and nucleic acid base residues⁸ have all been determined. Given these mean values, together with their standard deviations, it is easy⁸ to derive orthogonal coordinates for "standard residues". Apart from a variety of crystallographic uses, standard geometries are invaluable in model building, parameterization of empirical force fields, and interpretation of new structural data.

Substituent and Hybridization Effects. Early bond length tabulations⁵ were subdivided on the basis of gross differences in hybridization and environment. For example, hybridization changes at C* in I-III cause



appreciable bond length alterations, which are easily recognized in any individual crystal structure. Smaller changes in electron distribution—due, perhaps, to substitution and slight rehybridization—produce correspondingly smaller geometric variations, which are often close to the error limits of individual structure determinations. These are only discovered by the systematic analysis of many related structures. Studies of this type provide results that can be correlated with theoretical calculations, reactivity, spectral properties, and other physical phenomena. Two examples are discussed below.

Substituent-Induced Ring Deformations in Benzene. Early microwave and X-ray investigations showed that the regular hexagonal geometry of benzene is perturbed when the ring is substituted by strong electron-withdrawing or -donating groups. With reference to IV,



deformations due to electron-withdrawing groups involve an increase in the ipso angle α , a decrease in the ortho angles β , and shortening of bonds a with respect to bonds b. Deformations due to electron-donating groups are in the opposite sense. Only groups with strong electronic effects produce deformations that are consistently larger than the error limits of individual structure determinations.

The angular deformations ($\Delta\alpha$, $\Delta\beta$, $\Delta\gamma$, $\Delta\delta$ from 120°; see IV) in more than 100 mono- and para-disubstituted benzenes have been analyzed. Early results^{9,10} showed that $\Delta\alpha$ is the largest deformation, and that its value for a particular substituent X is unaffected by para-substitution; $\Delta\beta$ was found to be $\approx -\Delta\alpha/2$. Values of α were determined for a variety of substituents (Table II) by averaging relevant fragment geometries. It was recognized that σ -effects predominate in determining $\Delta\alpha$ values.^{10,11} This is consistent with the observed correlation between α and the electronegativity (χ) for

(6) Arnott, S.; Hukins, D. W. L. *Biochem. J.* 1972, 130, 453-465.

(7) Arnott, S.; Scott, W. E. *J. Chem. Soc., Perkin Trans. II* 1972, 324-335.

(8) Taylor, R.; Kennard, O. *J. Mol. Struct.* 1982, 78, 1-28. Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* 1982, 104, 3209-3212.

(9) Domenicano, A.; Vaciago, A.; Coulson, C. A. *Acta Crystallogr., Sect. B* 1975, B31, 221-234.

(10) Domenicano, A.; Vaciago, A.; Coulson, A. A. *Acta Crystallogr., Sect. B* 1975, B31, 1630-1641.

(11) Domenicano, A.; Mazzeo, P.; Vaciago, A. *Tetrahedron Lett.* 1976, 1029-1032.

Table II
Angular Deformations in Substituted Benzenes (IV)^{a,b}

X	α (mean), deg ^c	Linear regression values, deg ^d			
		$\Delta\alpha$	$\Delta\beta$	$\Delta\gamma$	$\Delta\delta$
N(Me) ₂	117.2	-2.4 (3)	0.6 (2)	1.4 (2)	-1.7 (3)
Ph	117.6	-2.3 (2)	1.0 (1)	0.6 (1)	-0.9 (2)
Me	118.1	-1.9 (2)	1.0 (1)	0.4 (1)	-0.8 (2)
CH=CHR	118.0	-1.8 (2)	0.8 (1)	0.3 (1)	-0.4 (2)
COMe	118.8	-1.0 (2)	0.4 (1)	0.2 (1)	-0.3 (2)
COOH	119.8	0.1 (2)	-0.2 (1)	0.1 (1)	0.2 (2)
OMe	119.9	0.2 (2)	-0.6 (1)	1.1 (1)	-1.1 (2)
CN	121.8	1.1 (2)	-0.8 (1)	0.3 (1)	-0.1 (2)
Cl	121.4	1.9 (2)	-1.4 (1)	0.6 (1)	-0.2 (2)
NO ₂	122.1	2.9 (2)	-1.9 (1)	0.3 (1)	0.4 (1)
F	123.4	3.4 (2)	-2.0 (1)	0.5 (1)	-0.4 (2)

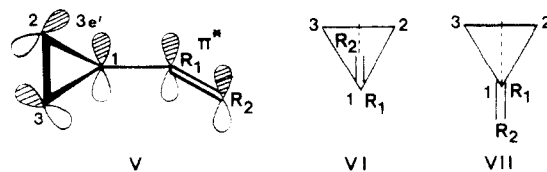
^a Standard deviations in α (mean) are in the range 0.1-0.2°. ^b Substitution reduces perfect D_{6h} ring symmetry to C_{2v} ; hence $\Delta\alpha + 2\Delta\beta + 2\Delta\gamma + \Delta\delta = 0$. ^c Reference 11.

^d Reference 13.

first-row functional groups¹¹ and second-row elements¹⁰ (Figure 2a,b). Later,¹² it was realized that substituents that interact with the benzene π -system also produce significant deformations ($\Delta\gamma$, $\Delta\delta$). Factor analysis showed that *all* substituent-induced deformations can be ascribed to two independent effects, which were interpreted as σ - and π -interactions.¹³ Values of $\Delta\alpha$, $\Delta\beta$, $\Delta\gamma$, $\Delta\delta$ for 21 functional groups were derived by linear regression, the geometries of 71 mono- and para-disubstituted benzenes (Table II)¹⁴ being used.

The marked sensitivity of α to σ -effects, evidenced by the α - χ plots, is confirmed by the plot^{11,13} of $\Delta\alpha$ against the Taft¹⁵ inductive parameter, σ_I (Figure 2c). The sensitivity of γ to π -effects is shown by the $\Delta\gamma$ - σ_R° plot¹³ in Figure 2d (σ_R° = Taft resonance parameter¹⁵). These correlations suggest that Δ -values may be a useful addition to traditional reactivity parameters, since they measure substituent effects on the ring in the ground state, do not depend on the choice of a suitable reaction series, are independent of solvent effects, and can be related to conformational changes.

Conjugation and Hybridization in Three-Membered Rings. Cyclopropane is unusual among cycloalkanes in that it conjugates with π -acceptor substituents,¹⁶ as is shown by spectroscopic results¹⁷ and the stabilization of carbonium ions by cyclopropane. Molecular orbital theory suggests¹⁸ that conjugation involves transfer of electron density from the cyclopropane $3e'$ orbitals to the π^* orbitals of the substituent (V). This would be



(12) Domenicano, A.; Vaciago, A. *Acta Crystallogr., Sect. B* 1979, B35, 1382-1388.

(13) Domenicano, A.; Murray-Rust, P. *Tetrahedron Lett.* 1979, 2283-2286.

(14) A similar independent analysis is described by: Norrestam, R.; Schepper, L. *Acta Chem. Scand. Sec. A* 1981, A35, 91-103. The two sets of angle deformations have a correlation coefficient of 0.966 and a root mean square deviation of 0.22°.

(15) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* 1973, 10, 1-80.

(16) Charton, M. "The Chemistry of Alkenes"; Zabicky, J., Ed.; Interscience, London, 1970; Vol. II, pp 511-610.

(17) Pete, J.-P. *Bull. Soc. Chim. Fr.* 1967, 357-370.

(18) Hoffmann, R. *J. Chem. Phys.* 1964, 40, 2480-2488. Hoffmann R.; Stohrer, W.-D. *J. Am. Chem. Soc.* 1971, 93, 6941-6948.

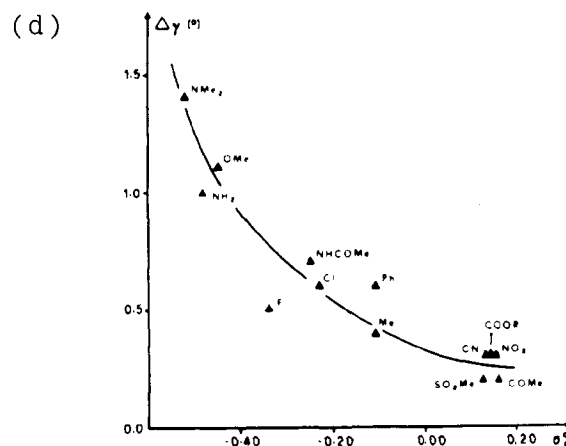
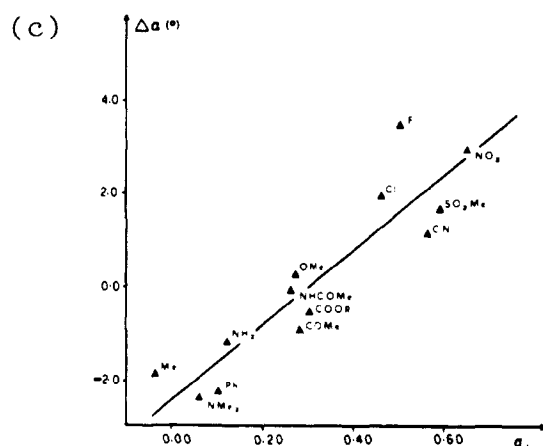
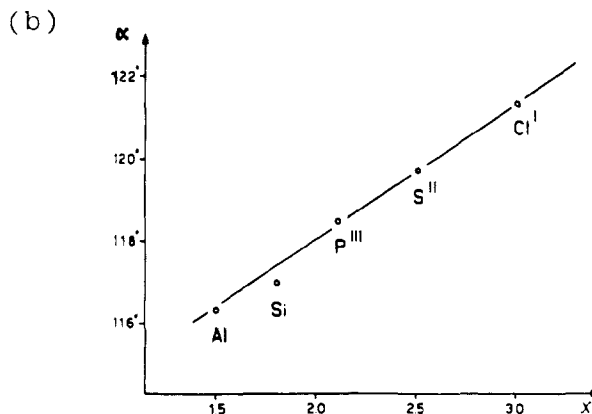
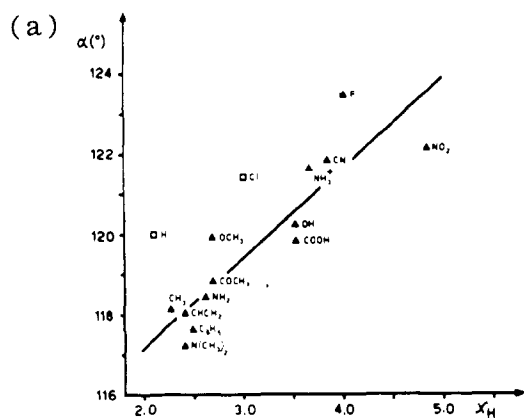
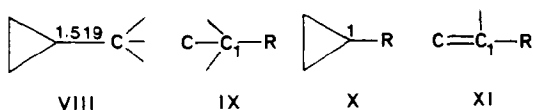


Figure 2. Correlation of substituent-induced angular deformations in benzene with electronegativity (χ) and Taft parameters (σ). The ipso angle (α in IV) is plotted (a) against χ for first-row functional groups (Reprinted with permission from ref 11. Copyright 1976, Pergamon Press Ltd.) and (b) against χ for second-row elements (Reprinted with permission from ref 10. Copyright 1975, International Union of Crystallography). In (c) the deformation $\Delta\alpha$ is plotted against the inductive parameter σ_I (Reprinted with permission from ref 13. Copyright 1979, Pergamon Press Ltd.), while in (d) the deformation $\Delta\gamma$ is plotted against σ_R (Reprinted with permission from ref 13. Copyright 1979, Pergamon Press Ltd.). We gratefully acknowledge permission to reproduce these plots from Dr. Aldo Domenicano and the copyright holders.

expected to shorten the distal (2-3) bond by δ and increase the vicinal (1-2,1-3) bonds by $\sim\delta/2$. However, the degree of conjugation will depend on the extent of orbital overlap, which is maximized in the cis- and trans-bisected conformations (Newman projections VI and VII, respectively).¹⁹

In order to quantify these effects, Allen²⁰ analyzed results from 146 X-ray studies of cyclopropane derivatives. The mean geometry of nonconjugated cyclopropanes was established by using purely C(sp³) derivatives (VIII). Substituent-induced bond length



asymmetries were consistently observed in the geometries of derivatives involving the π -acceptor substituents $-\text{C}=\text{O}$ (ketones, acids, esters; see Figure 1g for a typical geometrical tabulation), $-\text{C}=\text{C}$, and $-\text{CN}$. It was found that multiple substitution produces net distortions

Table III
Asymmetry Parameter^a for
Cyclopropane Rings Having π -Acceptor Substituents

subst.	δ , Å	subst.	δ , Å
C=O	-0.026 (5)	N=C	-0.018 (-)
C=C	-0.022 (4)	CN	-0.017 (2)
Ph	-0.018 (-)	N=N	-0.014 (-)

^a Reference 20.

tions that can be approximated by simple sums of individual substituent effects. The bond length asymmetry parameters (δ in the preceding paragraph) due to some representative substituents are given in Table III. The variation of bond length asymmetries with conformation suggests^{20,21} that conjugative overlap of ring and acceptor orbitals is effective for $-\text{C}=\text{O}$ and $\text{C}=\text{C}$ conformations within 30° of the bisected positions (VI, VII). These results are in agreement with ultraviolet spectral data.¹⁷

Cyclopropane is also unusual because its protons exhibit vinylic properties.¹⁶ This is consistent with the

(19) Hoffmann, R. *Tetrahedron Lett.* 1970, 2907-2909. Hoffmann, R.; Davidson, R. B. *J. Am. Chem. Soc.* 1971, 93, 5699-5705.

(20) Allen, F. H. *Acta Crystallogr., Sect. B* 1980, B36, 81-96.

(21) Allen, F. H. In "Molecular Structure and Biological Activity"; Griffin, J. F., Duax, W. L., Eds.; Elsevier Biomedical: New York, 1982; 105-116.

Table IV
Variation in the C(1)-R Bond Length^a in IX-XI due to Changes in Hybridization (*h*) and to Conjugative Effects (*c*)

R	fragment	IX X XI			<i>h</i> (Δ) ^b	<i>h</i> (sp ²) ^b	
		IX	X	XI			
C sp ³	<i>h</i>	1.538	1.519	1.507	-0.019	-0.031	
	C=C	<i>h</i>	1.507	1.480	1.472	-0.027	-0.035
		<i>h</i> + <i>c</i>		1.470	1.458		
C=O	<i>c</i>		-0.010	-0.014			
	<i>h</i>	1.512	1.489	1.482	-0.023	-0.030	
	(keto) <i>h</i> + <i>c</i>		1.474	1.460			
C=O	<i>c</i>		-0.015	-0.022			
	<i>h</i>	1.514	1.504	1.497	-0.010	-0.017	
	(acids, esters) <i>h</i> + <i>c</i>		1.484	1.470			
	<i>c</i>		-0.020	-0.027			

^a Reference 22. ^b $h(\Delta) = h(X) - h(IX)$, $h(sp^2) = h(XI) - h(IX)$ for each substituent R (see text).

abnormally short exocyclic C-C bond in derivatives of the type VIII (cf. I, II).^{20,22} Theoretical models²³ indicate that the C(ring) hybrid involved in the exocyclic C-C bond in VIII is $\sim sp^2$, whereas those involved in the ring σ -bonds are $\sim sp^3$. Hybridization in cyclopropane was studied in detail²² by comparing the C-R distances in the related fragments IX-XI (R = C(sp³), vinyl, keto, acid, ester). In those cases where conjugation can occur (i.e., X and XI with R = -C=C or -C=O), two C-R distances were obtained, for (i) conformations outside the ranges established for effective conjugation (this is a measure of hybridization effects (*h*)) and (ii) conjugative conformations, where C-R is further shortened by π -effects (*c*). Representative results are given in Table IV. The relative bond length contractions due to hybridization, defined by

$$h(\Delta) = [R-C(\text{cyclopropane})]_h - [R-C(sp^3)]$$

$$h(sp^2) = [R-C(sp^2)]_h - [R-C(sp^3)]$$

can be used to infer the hybridization of the cyclopropane ring atoms. Values of $h(\Delta)/h(sp^2)$ range from 59 to 77%. The mean, 69%, corresponds to $sp^{2.25}$ hybridization (30.8% s character) in exocyclic bonds; hence, ring σ -hybrids are $sp^{4.20}$ (19.2% s). Table IV also permits comparison of the relative conjugative abilities of cyclopropane and the vinyl group.¹⁶ The ratios $c(\Delta)/c(sp^2)$ average to 71%, which compares well with a UV bathochromic shift ratio of $\sim 60\%$.¹⁷

Conformational Analysis. Comparative reviews of steroids,²⁴ alkaloids and terpenes,²⁵ and medium rings²⁶ illustrate the extensive application of crystallographic data to conformational analysis.²⁷ In the present review, we are particularly concerned with the systematic analysis of solid-state conformations. Although some molecules are known to adopt different conformations in solution and in the crystalline state, it has been shown that solid-state conformational data can be successfully related to solution properties, provided that a sufficient number of crystal structures are studied.

(22) Allen, F. H. *Acta Crystallogr., Sect. B* 1981, B37, 890-900.

(23) Bennett, W. A. *J. Chem. Educ.* 1967, 44, 17-24 and references therein.

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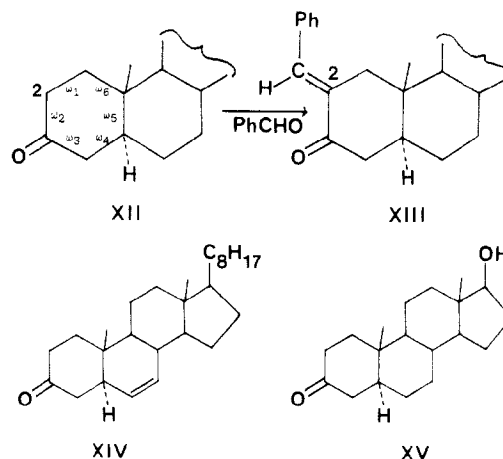
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This is illustrated by the following example.

The relative rates of condensation with benzaldehyde of a series of 3-keto-5 α steroids (XII) were determined



by Barton et al.²⁸ The 2-benzylidene ketone XIII is exclusively formed by elimination of OH⁻, the reaction involving rehybridization of C(2) from sp³ to sp². The presence of ethylenic links and/or substituents at positions remote from the reaction center was found to produce large differences in reaction rates. It was therefore inferred that gross conformational changes at remote sites produce small changes—here at C(2)—by "conformational transmission". This influences the rate of condensation, *r*, which may be expressed as²⁸

$$r = r_0 \prod f_i$$

where *r*₀ is the rate for saturated XII and the *f*_{*i*} are "group rate factors" for remote substituents or double bonds.

The crystal structure²⁹ of cholest-6-en-3-one (XIV), which has the highest reaction rate (*r* = 645), shows an unusually flat A ring, with a mean ring torsion angle $\bar{\omega}$ ($=\sum_i \omega_i/6$ in XII) of only 50.4°. The flattening is especially pronounced at C(2), where ω_{12} ($=(\omega_1 + \omega_2)/2$ in XII) is 42.2°. The ring bond angle at C(2), ν , is correspondingly high at 114.4 (8)°. In contrast, the structure³⁰ of 17 β -hydroxyandrost-3-one (XV), which has a much lower reaction rate (*r* = 188), shows $\bar{\omega}$ = 54.1°, ω_{12} = 51.7°, and ν = 110.7°. Clearly, C(2) is more prepared to undergo rehybridization in XIV than in XV.²⁹ An analysis²¹ of several other A-ring conformations confirmed that the reaction rate tends to increase as the ring becomes flattened at C(2). The parameter $\alpha = \omega_{12} - \bar{\omega}$ was used to express the relative puckering in each ring (negative α represents flattening at C(2)). For steroids with *r* = 33, 188, 235, and 645, the corresponding mean values of α were 2.6, -2.8, -3.3, and -8.3°. Although the data are limited, the *r*- α correlation is qualitatively acceptable.

Systematic Analysis of Intermolecular Interactions

Hydrogen-Bonding Studies. Systematic analyses of crystal structures have made a significant contribution to our knowledge of hydrogen bonding. Studies of O-H...O and C-H...O bonds are discussed below.

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