INTERPRETATION OF THE PATTERSON FUNCTION OF CRYSTALS CONTAINING A KNOWN MOLECULAR FRAGMENT. THE STRUCTURE OF AN *ALSTONIA* ALKALOID[1]

Sir:

The interpretation of the Patterson function can be greatly facilitated if the molecules composing the crystal contain a rigid group of atoms with a known internal geometry. We wish to outline a computer procedure by which the known presence of such a group can be exploited to yield a refinable approximation to the crystal structure.

The unit cell coördinates (x_0, y_0, z_0), $(x_1, y_1, z_1), \cdots$, $(x_{n-1}, y_{n-1}, z_{n-1})$ of the n atoms in the rigid group are expressible in terms of six parameters: the coördinates (x_0, y_0, z_0) of a point in the group, and the Euler angles ϕ, θ, ψ, defining the orientation of the group with respect to a Cartesian coördinate system, fixed in relation to the crystal axes. A practical computer procedure for determining the probable values of these parameters is a two-stage search of the Patterson function. The first stage computes a modified minimum function[2]

$$M_p(\phi,\theta,\psi) = \text{Min}\{P_1, P_2, \cdots, P_p\}$$

with $p = n(n-1)/2$, where the P's are the values of the Patterson function at the vertices of the p vectors between the n atoms of the group. The "most probable" values of ϕ, θ and ψ are the coördinates of the highest peak in this three-dimensional function. The second stage executes a similar search of the Patterson function with all vectors between the group in orientation (ϕ,θ,ψ) and its symmetry-related groups in the unit cell. The number, q, of such vectors depends on the number of symmetry-related groups, *i.e.*, on the multiplicity of the positions of the space group. The function $M_q(x_0, y_0, z_0)$ is less than three-dimensional whenever the space-group symmetry allows the origin to be arbitrarily specified in one or more dimensions. The coördinates of the maximum in $M_q(x_0, y_0, z_0)$ are the tentative values of the translational parameters x_0, y_0, z_0. If the peak value of $M_q(x_0, y_0, z_0)$ is less than that of $M_p(\phi\theta\psi)$, an improved fit, by the minimum criterion, may be accomplished by trial and error adjustment of ϕ, θ, and ψ so as to maximize $M_{p+q}(\phi,\theta,\psi,x_0,y_0,z_0) = \text{Min}\{M_p(\phi\theta\psi), M_q(x_0,y_0,z_0)\}$.

Having thus deduced a set of approximate coördinates for the rigid-group atoms the rest of the structure can be explored by means of multiple Patterson superposition techniques.

We have used this approach to determine the structure of Alkaloid C (m.p. 168–169°. $[\alpha]^{25}D$ +200° for $c = 1.0$ in ethanol) from *Alstonia Muelleriana*, first isolated by Gilman,[3] and characterized by him as having the approximate composition $C_{19-20}H_{20}O_3N_2$, and giving an ultraviolet spectrum indicating the presence of an oxindole group. Crystals of this com-

(1) Support of this investigation by Grant G-21408 from the National Science Foundation, and by Grant H-4179 from the National Heart Institute, U. S. Public Health Service, is gratefully acknowledged.

(2) M. J. Buerger, "Vector Space," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 242.

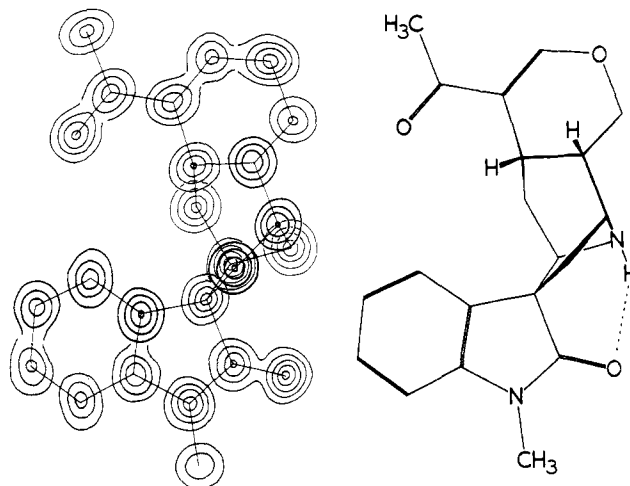(3) R. E. Gilman, Ph.D. Thesis, University of Michigan, 1959.

Fig. 1.—Electron density distribution and structure of the molecule.

pound are monoclinic, space group $P2_1$, containing two molecules per unit cell of dimensions $a = 9.09$ Å., $b = 13.11$ Å., $c = 7.14$ Å. and $\beta = 95°8'$. The crystal structure was determined using 1437 photographically recorded and integrated reflections.

A rotational and translational search of Patterson space was carried out using the vectors, respectively, within and between the ten atom ($n = 10$) oxindole groups of known internal geometry.[4] The rotational minimum function $M_{45}(\phi\theta\psi)$ showed two dominant peaks, whose relative positions corresponded, very nearly, to a 180 degree rotation about an axis along the carbon–oxygen bond, reflecting the near twofold symmetry of the oxindole group about this axis. The higher one of the two peaks was subsequently found to represent the correct orientation. The two-dimensional function $M_{55}(x_0, z_0)$ for the $q = n(n+1)/2 = 55$ independent vectors from the oxindole group in orientation $(\phi\theta\psi)$ to its screw-axis related group unambiguously gave the location of the two groups relative to the 2_1 screw axis. Finally a 20-fold Patterson superposition $M_{20}(xyz)$ was computed using the atom coördinates of the two oxindole groups. This yielded the positions of all remaining carbon, nitrogen and oxygen atoms; their respective chemical identity was brought out by the subsequent least-squares refinement. Difference Fourier syntheses calculated following several cycles of refinement revealed all hydrogen atoms. Using anisotropic thermal parameters for the non-hydrogen atoms the refinement continued to $R = 0.062$. The empirical formula is $C_{20}H_{22}O_3N_2$. Figure 1 shows the electron density distribution and the relative configuration of the molecule. The absolute configuration chosen for the figure is the one whose $C(15)$ configuration is the same as that deduced for ajmalicine.[5] A fuller account of the results will be presented elsewhere.

The calculations were performed on an IBM 7090 computer. The Patterson function with origin peak removed, sharpened by $\exp(4.5 \sin^2\theta/\lambda^2)$, and computed on a $15 \times 15 \times 60$ grid, was stored in the magnetic core storage using a packed word format. A total of about 150 minutes of computer time was used for the three searches of Patterson space, that is, for deducing the complete, refinable trial structure from the Patterson function. In retrospect it is clear that the computing time could have been reduced by at least a factor

(4) H. Pandraud, *Acta Cryst.*, **14**, 901 (1961).

(5) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474 (1959); E. Wenkert, B. Wickberg and C. L. Leicht, *ibid.*, **83**, 5037 (1961); M. Shamma and J. B. Moss, *ibid.*, **83**, 5038 (1961).

of two without risk of overlooking any significant peaks in the minimum functions.

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RECEIVED DECEMBER 17, 1962

THE MECHANISM OF BENZYLIC BROMINATION WITH N-BROMOSUCCINIMIDE

Sir:

Studies pertaining to allylic brominations or the apparently analogous benzylic brominations by N-bromosuccinimide (NBS) have been widely accepted as supporting a free-radical chain mechanism involving succinimidyl radicals as the chain-carrying species.[1] The chief alternative to this pathway, one involving free bromine, was originally suggested by Goldfinger,[2] and has been promulgated by Sixma and Riem[3] and by McGrath and Tedder.[4]

NBS has been rejected on the basis of the studies of Dauben[5-7] and of work by Kooyman,[9] who determined the relative reactivities of a series of substituted toluenes toward bromine and NBS. Both series of reactions obeyed the Hammett correlation, but yielded different values of the reaction constant, rho (-1.55 for NBS and -1.05 for bromine). The postulation of a common hydrogen abstracting species for the two reactions, namely, Br·, would demand identical rho values.

We have determined the relative reactivities of a series of substituted toluenes toward NBS, N-bromo-tetrafluorosuccinimide (NBTFS), N-bromotetra-methylsuccinimide (NBTMS), and molecular bromine, in benzene solution at 80°, and have found all values of the reaction constants to be identical within the limits of experimental error. Further examination of the last two brominating agents at 19° reveals that they also display identical rho values at this temperature.

TABLE I

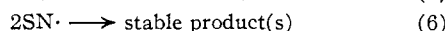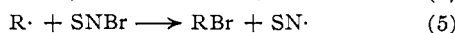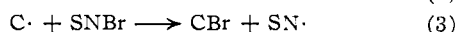RELATIVE RATES[a] FOR THE BROMINATION OF SUBSTITUTED TOLUENES LOG k_{rel}. FOR INDICATED SUBSTITUENT

Brominating agent	p-OCH₃	p-CH₃	p-C(CH₃)₃	p-Cl	m-Br	p-CN	T, °C.	ρ[b]	r[c]
NBS	1.093	0.418	0.464	−0.145		−0.953	80	−1.46 ± 0.07	0.996
NBTFS		.500	.457	− .081		− .875	80	−1.45 ± .07	.996
NBTMS	0.980	.480	.402	− .168	−0.616	− .845	80	−1.36 ± .05	.997
Br₂	0.956	.383	.393	− .138	− .650	− .914	80	−1.36 ± .05	.996
NBTMS		.530		− .168	− .761		19	−1.79 ± .08	.996
Br₂		.506	.551	− .125	− .703		19	−1.76 ± .12	.994

[a] Rates relative to toluene were determined by the study of competitive reactions using quantitative n.m.r. spectroscopy for the requisite product analyses. An integrated rate expression was utilized for the calculations.[11] [b] Uncertainties are expressed as standard deviations. [c] Correlation coefficient.

The most extensive mechanistic studies of the allylic bromination reaction have been reported by Dauben and his students,[5-7] who have established the radical chain character of the reaction and have determined the over-all kinetics of the bromination of cyclohexene. For the brominations initiated by the decomposition of 2,2'-azo-bis-isobutyronitrile (AIBN), the rate of disappearance of NBS depends upon the concentrations of reactants according to equation 1.

$$-d[NBS]/dt = k[NBS]^0[RH]^1[AIBN]^{1/2} \quad (1)$$

This rate expression corresponds to that derived from these reactions (where C· = initiator fragment; SNBr = N-bromosuccinimide; and RH = hydrocarbon substrate)

$$AIBN \longrightarrow 2C· \quad (2)$$
$$C· + SNBr \longrightarrow CBr + SN· \quad (3)$$
$$SN· + RH \longrightarrow SNH + R· \quad (4)$$
$$R· + SNBr \longrightarrow RBr + SN· \quad (5)$$
$$2SN· \longrightarrow stable\ product(s) \quad (6)$$

No corresponding studies have been attempted on benzylic systems, nor have any comparisons been made between benzylic and allylic systems which allow one to state whether or not the same mechanism operates in both cases for brominations by NBS.

Although N-chlorosuccinimide is thought to serve in chlorination reactions only to provide a low, constant concentration of molecular chlorine,[2,8] a similar role for

All data fit the Hammett correlation best when σ^+ values are utilized. Application of standard statistical methods[10] to the data shows that when all series of data at each temperature are treated as belonging to the same set, the fit to a straight line is at least as good as for each of the individual series (see Table I). At 80°, $\rho = -1.39 \pm 0.03$ and at 19°, $\rho = 1.78 \pm 0.06$. For both cases, the correlation coefficients are 0.995.

The identity of the rho values for this widely differing series of brominating agents forces us to conclude that the same radical serves as the hydrogen abstractor in every case.[12] Supporting evidence can be found in the data of Wiberg and Slaugh,[13] who discovered that reactions involving NBS and bromine exhibit essentially the same kinetic isotope effect in the removal of α-hydrogens from toluene.

Any other conclusion would necessitate arguing that identical rho values for four different brominating agents, and identical temperature dependence of rho for two of them, is strictly coincidental. This means postulating that changes in structure of the attacking radical have essentially no effect on its sensitivity to the polar effect. Such a postulate lacks support from consideration of the different values of rho found for radical attack at the side chain of toluene, values of which vary from -0.6 through -1.8.[14-16] Hydrogen abstraction from substituted benzaldehydes has been found to be sensitive to the structure of the

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(6) H. J. Dauben, Jr., and L. L. McCoy, *J. Org. Chem.*, **24**, 1577 (1959).
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(9) E. C. Kooyman, R. van Helden and A. F. Bickel, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **56B**, 75 (1953).
(10) H. H. Jaffé, *Chem. Revs.*, **53**, 253 (1953).
(11) C. Walling and B. Miller, *J. Am. Chem. Soc.*, **79**, 4181 (1957).
(12) A similar conclusion has been reached through selectivity studies on benzylic halogenations leading to secondary and tertiary bromides. Private communication from Professor G. A. Russell, Iowa State University.
(13) K. B. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.*, **80**, 3033 (1958).
(14) C. Walling, ref. 1, pp. 418, 366.
(15) C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, **82**, 6113 (1960).
(16) E. S. Huyser, *ibid.*, **82**, 394 (1960).