

4.8×10^{-4} l. mole⁻¹ sec.⁻¹; a value of 4.77×10^{-4} l. mole⁻¹ sec.⁻¹, taken in conjunction with a value for $k_c/(k_a + k_b)$ of 75 l. mole⁻¹, gives excellent agreement between the calculated and experimental k_2° values.

Table I. Correlation of Calculated and Experimental Second-Order Rate Coefficients, k_2° (l. mole⁻¹ sec.⁻¹), for Reaction of Methyl Chloroformate with Silver Nitrate in Acetonitrile at 25.0°

[AgNO ₃]	α	$10^4 k_2^\circ$, exptl.	$10^4 k_2^\circ/\alpha$	$10^4 k_2^\circ$, calcd.
0.00100	0.94	2.23	2.4	2.06
0.00200	0.89	2.12	2.4	2.08
0.00500	0.79	2.13	2.7	2.08
0.0100	0.69	1.96	2.8	2.03
0.0200	0.57	1.82	3.2	1.87
0.0400	0.45	1.68	3.7	1.62
0.0800	0.35	1.32	3.8	1.36
0.160	0.26	1.08	4.2	1.07

The values for k_2 of 4.77×10^{-4} l. mole⁻¹ sec.⁻¹ and for $k_2 k_b/(k_a + k_b)$ of 2.00×10^{-4} l. mole⁻¹ sec.⁻¹ show that in acetonitrile at 25.0°, and in the absence of any silver ion assistance to chloride ion removal, an intermediate anion has a 0.42 probability of decomposing by loss of chloride ion and a 0.58 probability of decomposing by loss of nitrate ion.

When 0.0100 *M* silver perchlorate was added to a 0.0100 *M* solution of silver nitrate reacting with 0.0935 *M* methyl chloroformate, the integrated k_2° values (based on stoichiometric nitrate ion concentration) fell in value as reaction proceeded; the initial k_2° value was 1.83×10^{-4} l. mole⁻¹ sec.⁻¹. Although the addition of silver perchlorate will increase the partitioning of the intermediate to products, an accompanying reduction in the concentration of dissociated nitrate ion will decrease the rate of formation of the intermediate.

The success of the theoretical analysis can be taken as an excellent additional evidence⁵ for the formation in nucleophilic substitution reactions at carbonyl carbon of an actual intermediate anion, capable of in part reverting to reactants. For suitable replacements of halogen attached to a carbonyl carbon, the treatment allows calculation of the proportions of the intermediate anion which revert to reactants and which go on to give products by loss of halide ion.

Acknowledgment. The authors are grateful to the Petroleum Research Fund of the American Chemical Society for partial support of this work.

(5) (a) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951); (b) for a very recent review, see T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 4886 (1964).

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The Crystal and Molecular Structures of 7-Chloro- and 7-Bromo-4-hydroxytetracycloxide

Sir:

The synthesis of a new class of tetracyclines,¹ called "tetracycloxides," was recently reported.^{2,3} This com-

(1) R. C. Esse and G. M. Sieger, South African Patent Application 63/4791 (filed Oct. 22, 1963, accepted March 25, 1964).

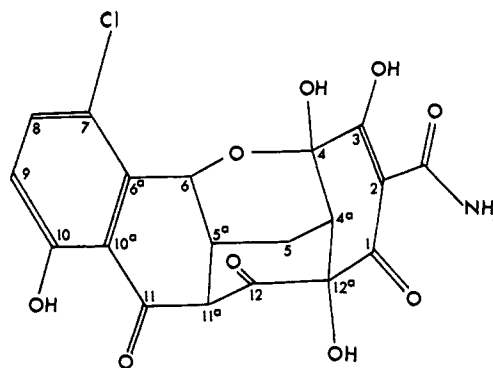


Figure 1. 7-Chloro-4-hydroxytetracycloxide.

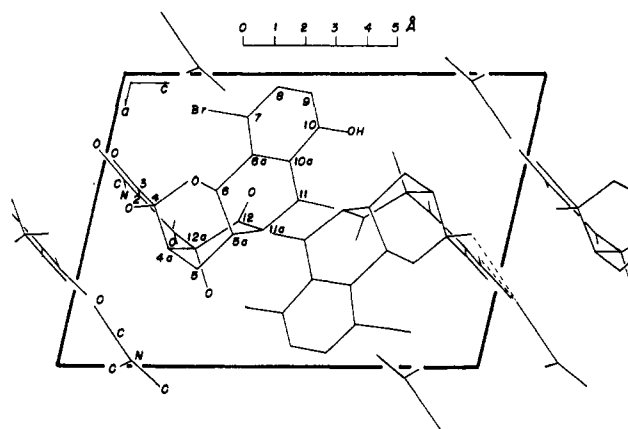


Figure 2. Projection of the unit cell along the *b*-axis.

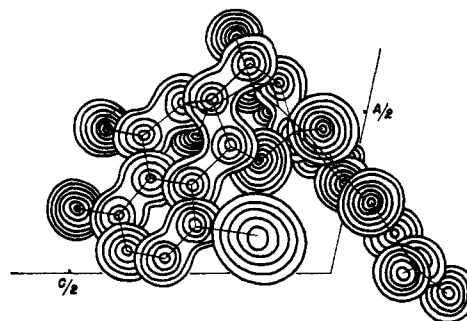


Figure 3. Composite electron density map showing one asymmetric unit: contours at 1 e Å.⁻³ (for bromine, 5 e Å.⁻³), zero contour omitted.

munication represents a preliminary account of the results of the single crystal X-ray analysis of two halogenated tetracycloxides. This work was undertaken to verify unambiguously the proposed structure for these compounds, especially the presence of the C(4)-O-C(6) hemiketal link.

Single crystals of 7-chloro- (I) and 7-bromo-4-hydroxytetracycloxide (II) found to be solvated with dimethylformamide (DMF) were obtained *via* the vapor-phase transfer method using DMF as the solvent and water as the transfer agent. The crystals obtained

(2) R. C. Esse, J. A. Lowery, C. R. Tamorria, and G. M. Sieger, *J. Am. Chem. Soc.*, **86**, 3874 (1964).

(3) R. K. Blackwood and C. R. Stephens, *ibid.*, **86**, 2736 (1964).

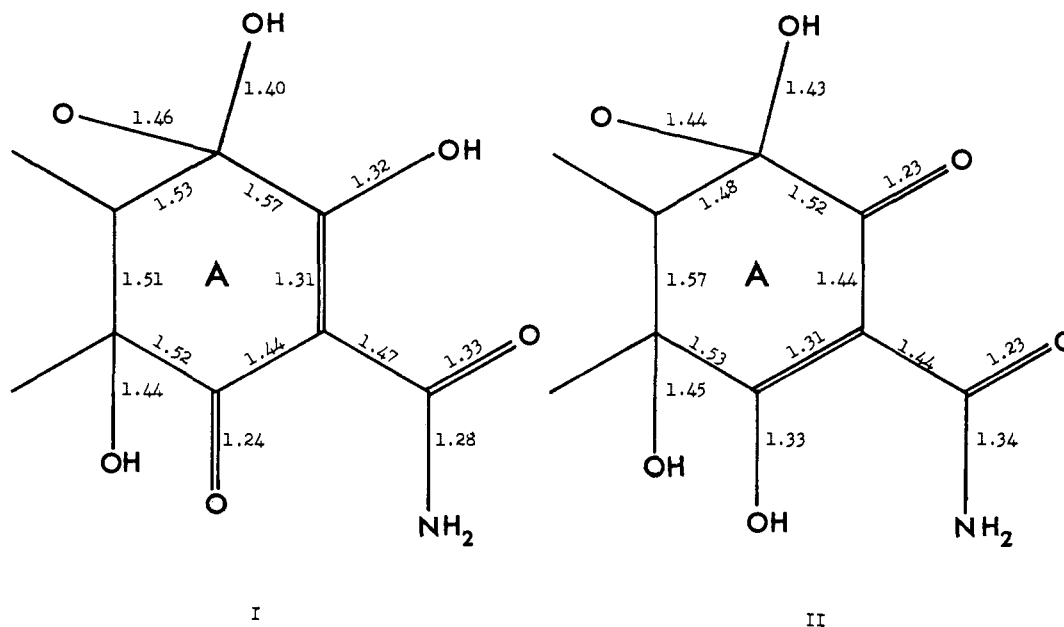


Figure 4. Bond distances relating to ring A.

for both compounds were shown to be monoclinic with the dimensions of the unit cell for the chloro and bromo derivatives being $a = 9.46 \text{ \AA}$, $b = 9.30 \text{ \AA}$, $c = 13.48 \text{ \AA}$, $\alpha = \gamma = 90^\circ$, $\beta = 104.0^\circ$, and $a = 9.47 \text{ \AA}$, $b = 9.30 \text{ \AA}$, $c = 13.54 \text{ \AA}$, $\alpha = \gamma = 90^\circ$, $\beta = 103.4^\circ$, respectively. The crystals are isomorphous and their space group is $P2_1$ with two molecules per unit cell, the empirical formulas being $C_{22}H_{21}N_2O_{10}Cl$ and $C_{22}H_{21}N_2O_{10}Br$, respectively. Density measurements and vapor phase chromatography indicated the presence of 1 mole of DMF as solvate.⁴

Intensity data were obtained using the stationary crystal-stationary counter technique employing balanced filters and pulse-height discrimination on a General Electric XRD-6 diffractometer. For I, of the 1421 reflections accessible to 1 \AA . resolution, 1390 (97.8%) were taken to be observable. For II, these numbers were 1046 and 1233 (87.7%), respectively.

The structure of the bromo derivative was solved using the heavy-atom method. The input parameters to the Patterson function were sharpened with $[Z_{Br}/\{f_{Br} \cdot \exp(2 \sin^2 \theta/\lambda^2)\}]$ to enhance the heavy atom vectors (where Z_{Br} and f_{Br} are the atomic number and scattering values of bromine, respectively). The positions of the bromine atoms were readily obtained, and a first density map, based on the phases as determined by the bromine atoms only, revealed the position of a molecular skeleton containing 17 lighter atoms. All significant peaks were larger than $2 e \text{ \AA}^{-3}$ and they could be inferred to represent the rings C and D of the tetracycline system as well as a third ring. In a second pass these atoms were included weighted as carbons in the structure factor calculations, which yielded a value for R ($\sum |F_o| - |F_c| / \sum |F_c|$) of 0.31. A subsequent density map revealed the positions of twelve additional atoms, which

in effect completed the tetracycloxide skeleton and substituents. A third density calculation then produced still another five peaks which were recognized as representing the DMF of solvation. At this stage the value of R had dropped to an encouraging 0.23. Four cycles of block-diagonal, isotropic, least-squares refinement yielded a drop in R to 0.13 for all observed reflections. The positional parameters thus obtained were subsequently used with the intensity data for I and four cycles of refinement produced for these data an R value of 0.11. Studies of electron density maps for both compounds indicated the presence of anisotropic thermal motion, especially for the heavy atoms, and additional refinement is planned.

The structure deduced by chemical means (see Figure 1) has been confirmed, as is shown in Figures 2 and 3, and the hemiketal-derived six-membered ring is in the chair conformation, as is ring B. Observations from a Dreiding model reveal that, if ring B were a boat conformer, the oxygen atoms attached to atoms 1 and 10 would be subjected to considerable steric hindrance. It appears that the enolization of the A ring of I differs from that for II. The bond distances and angles calculated indicate that the double bond which is present in this ring must, in the case of I, be assigned to C(2)-C(3) and for II to C(1)-C(2). In both instances double conjugation is maintained with a carbonyl group and the amide function, as is shown in Figure 4. Conclusions to be drawn from these observations will be deferred for future discussion.

The crystal structure is held together by an infinite chain of hydrogen bonds. The carbonyl group of the solvate participates in bifurcated hydrogen bonds to the 4-OH of one molecule of tetracycloxide ($O \cdots HO$ distance is 2.75 \AA) and the NH_2 group of the carboxamide function attached to a second molecule ($O \cdots HN$ distance is 2.90 \AA). The brittleness of the crystals may be attributed to the coplanarity of rings A and B and their functional groups, thus producing a large, easily dislodged area for van der Waals interactions between symmetry-related molecules.

(4) The author wishes to thank Dr. R. C. Esse of the Pharmaceutical Product Development Section, Lederle Laboratories, American Cyanamid Company, for supplying the samples, and Mr. C. Pidacks of the Organic Chemical Research Section, Lederle Laboratories, American Cyanamid Company, for demonstrating DMF of solvation by gas chromatography.

A more detailed account of the analysis will be submitted to *Acta Crystallographica*.

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Macrocyclic Polydimethylsiloxanes

Sir:

The possibility that macromolecular polycondensates may consist partially or wholly of large cyclic molecules has been raised repeatedly¹⁻³ and analyzed theoretically⁴ but never tested by observation. We have now obtained evidence for macrocyclic populations in dimethylsilicone (D) polymers and characterized their distribution.

Equilibrated polydimethylsiloxane mixtures were prepared by heating octamethylcyclotetrasiloxane (with or without added diluent) with traces of KOH. The reaction mixtures were decatalyzed and chain-stopped with trimethylchlorosilane-pyridine and fractionated by molecular distillation, solvent extraction, vapor phase chromatography (v.p.c.), and gel permeation chromatography (g.p.c.).⁵ Milligram quantities of the individual cyclics up to D₂₅ were collected by v.p.c. for spectroscopic characterization. The distribution curves, obtained either from the fractionation data or from high resolution g.p.c. tracings on the unfractionated equilibrates, showed that the isolated macrocyclics formed part of a continuous population that extended to at least D₄₀₀. This macrocyclic population, arbitrarily defined as the cyclics above D₁₂, was found to constitute 2-3% of the total polymer in commercial methylsilicone oils, gums, and rubbers; 8-10% of the total in systems equilibrated at 200-250 g./l. concentration; and probably 50-80% of the precipitated "polymer" fractions recovered⁶ in low yields from such equilibrates.

The molar cyclization constants, K_n , characterizing the stabilities of the n -unit rings, D _{n} , were calculated from the relation⁴

$$K_n = [D_n]_{\text{equil}} x^{-n} \\ = [D_n]_{\text{equil}} \left(\frac{\bar{P}_w - 1}{\bar{P}_w + 1} \right)^{-n}$$

where x and \bar{P}_w are, respectively, the degree of condensation and the weight-average degree of polymerization in the acyclic portion of the equilibrate. A plot of $\log K_n$ vs. $\log n$ (Figure 1) showed a stability maximum at D₄, a minimum at D₁₂, a second maximum at D₁₅,⁷ a region of steepening slope above the second maximum, and finally a straight line with a slope of $-2.86 (\pm 5\%)$ over the range D₄₀-D₂₀₀ and probably beyond.

The linear relationship observed for the largest

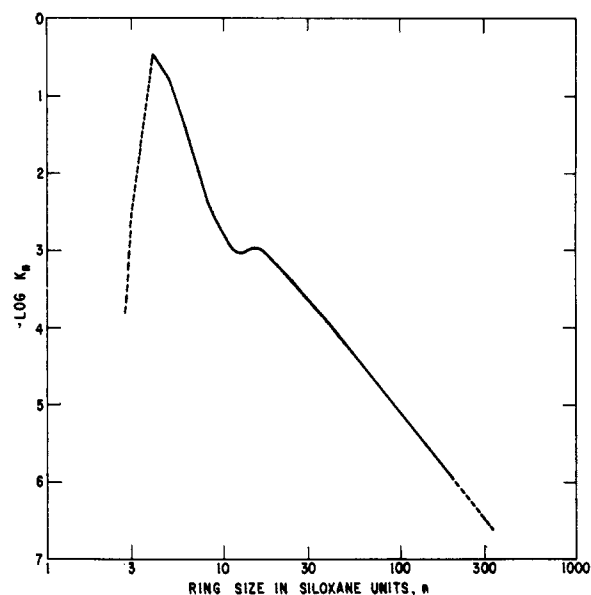


Figure 1. Dependence of molar cyclization constant, K_n , on number of siloxane units per ring, n , for polydimethylsiloxanes in toluene at 110°. The dotted portions of the curve are considered less reliable than the remainder.

rings apparently represents the first experimental verification of the Jacobson-Stockmayer cyclization theory.⁴ This predicts a dependence of K_n on $n^{-2.5}$ in a Θ solvent, but the treatment is easily extended to show a dependence on $n^{-(2+a)}$, where a is the exponent in the intrinsic viscosity-molecular weight relationship, in other solvents. Reported values of a for polydimethylsiloxane in toluene, admittedly at 25 rather than 110°, range from 0.59⁸ to 0.84.⁹ The deviations of the smaller-ring K_n values from the limiting line suggest, however, that the random distribution of end-to-end segment distances presumed by the theory is not attained until the chain segments are 70-80 atoms long.

The distribution of stabilities in the lower cyclic siloxanes shows a remarkable parallel to that in alicyclic rings containing *one-half* as many ring atoms. Thus, if one compares the K_n values for n -unit ($2n$ -atom) siloxane rings with the reported tendencies of α,ω -disubstituted aliphatics to yield n -atom ring esters,¹⁰ anhydrides,¹⁰ lactones,¹¹ or cycloalkanones,¹² one finds in each series a sharp maximum at an n of 4-6, corresponding to the smallest strainless ring; a minimum at 9-13; a second maximum, broader and weaker than the first, at 15-18; and a gradual decline beyond. This parallelism probably arises because the $-\text{CH}_2-$ and $-\text{O}_{1/2}\text{Si}(\text{CH}_3)_2\text{O}_{1/2}-$ repeating units, although quite different in size, are rather similar in shape, in steric requirements relative to interunit distances, and in preferences as to interunit angles. We suggest it is these geometrical characteristics of the repeating unit as a whole, rather than simply the numbers of

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(12) Whether *via* the Ruzica, Ziegler, Hunsdecker, diketene, or acyloin syntheses.