brosylate to A from *trans*-cyclopentyl brosylate. Using this value ($Y$) of the ratio of anti to syn elimination, the ratio of isotope effects a/d, a/c, etc., can also be calculated from the olefin yields. Table I gives the percentage of the elimination leading to the products A, B, and C from cis and trans deuterated reactants in various solvents. In ethanol–water solvents, anti elimination is found to be favored over syn by a factor of only 1.37, a relatively nonstereospecific process. This is consistent with our earlier conclusion that this is an E1 elimination process which proceeds from the intimate ion pair.[2] The results with sodium ethoxide in ethanol given in the last entry in the table show that the classical E2 reaction conditions favor anti over syn elimination by a factor of approximately six or more.[5]

It is reasonable that nucleophilic attack on the intimate ion pair proceeds with highly stereospecific inversion of configuration while proton elimination is not stereospecific; the leaving group can effectively shield the front side of the reacting carbon[6] but cannot effectively shield the two front-side $\beta$-hydrogens as well. If the cyclopentyl moiety of the intimate ion pair is assigned the planar carbonium ion structure, no strong stereoelectronic preference for trans elimination should obtain. On the other hand it is unreasonable to assume that substitution occurs *via* direct nucleophilic attack on the reactant (SN2) while elimination occurs in the ion pair. The observed $\alpha$-$d$ effect of 1.15 in ethanol,[2] accompanied by only 12% elimination, must be predominantly on the substitution reactions; no SN2 reactions are known which show isotope effects larger than about 1.04.[7]

From the ratios of isotope effects in elimination, calculated from the present work, and the isotope effects in Table X, ref 2, it is possible to estimate the individual $\beta$-$d$ effects a, b, c, and d. The primary effect "a" in ethanolysis is 1.72 and the secondary effects b, c, and d while subject to some error all appear inverse and range from 0.75 to around unity. The secondary effects are inverse presumably because elimination not only reduces the hyperconjugative demand but also forces the noneliminated $\beta$-hydrogen into an orientation unfavorable to hyperconjugation.

The results for solvolysis in TFE–W mixtures surprisingly indicate that syn elimination is favored over anti by a factor of about 4! This implies that elimination by the nonbasic solvent is sufficiently slow so that it is dominated at the ion pair stage by internal elimination of the $\beta$-hydrogen by the leaving group.[8] These results may require revision of our earlier analysis of this mechanism.[2] We must consider the possibility that internal elimination in the intimate ion pair competes with rate determining formation of the solvent separated ion pair. Additional experiments to elucidate this question are in progress.

Results on stereochemistry of elimination as well as isotope effects[3] and stereochemistry of substitution product formation[3] in D–W solvents indicate that solvolysis proceeds by mixed mechanisms involving both ion pairs as intermediates from which the products are derived.

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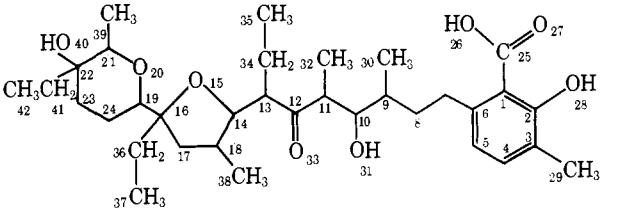
## A Structural Study on the Sodium Salt of the Ionophore, X-537A (Lasalocid), by X-Ray and Nuclear Magnetic Resonance Analysis

*Sir:*

The "ionophore" antibiotic X-537A, lasalocid (**1**),[1]



**1**

has been the subject of several solution[2,3] and crystallographic studies.[4–7] We now report the results of a combined X-ray and nmr study that suggests the importance of dimeric structures when considering the behavior and mode of action of this smallest member of the acidic ionophores.

In the course of trying to get crystals of a sodium salt of X-537A suitable for X-ray structure determination, we isolated two different crystalline forms of the sodium salt of 5-Br-X-537A (**2**). Crystal data are shown in Table I. Crystals of modification I could be grown from ethyl acetate solution but were obtained in greatest abundance from the nonpolar carbon tetrachloride. Some crystals of modification II were obtained from ethyl acetate, but they were also obtained in high yield from acetone. Full X-ray structure analyses have been carried out on both forms. Stereoscopic pictures of the two structures are shown in Figures 1 and 2. In both cases the structures of the $Na^+$ salts are dimeric; however, the mode of assembly of the dimer is different in the two cases. If one calls the phenyl ring the "head" of the circular X-537A entity and the oxacyclohexane ring the "tail,"[4] then form I is "head" to

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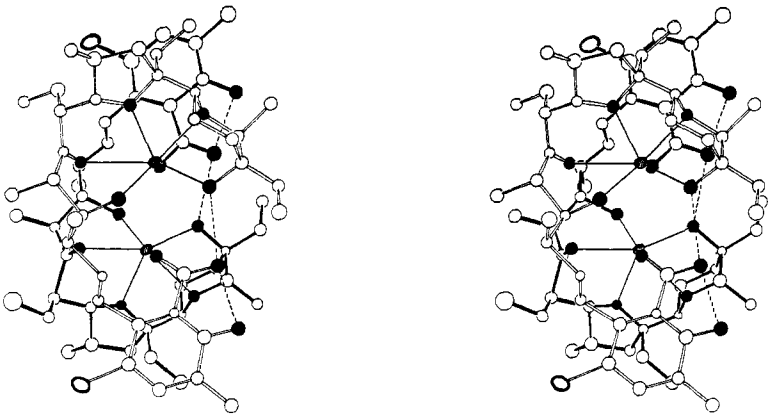

Figure 1. Stereoscopic view of the "head" to "tail" structure of the dimer of $Na^+$ salt of 5-Br-X-537A in crystal modification I. Oxygen atoms are shown as dark spheres, the sodium ions by line shading.

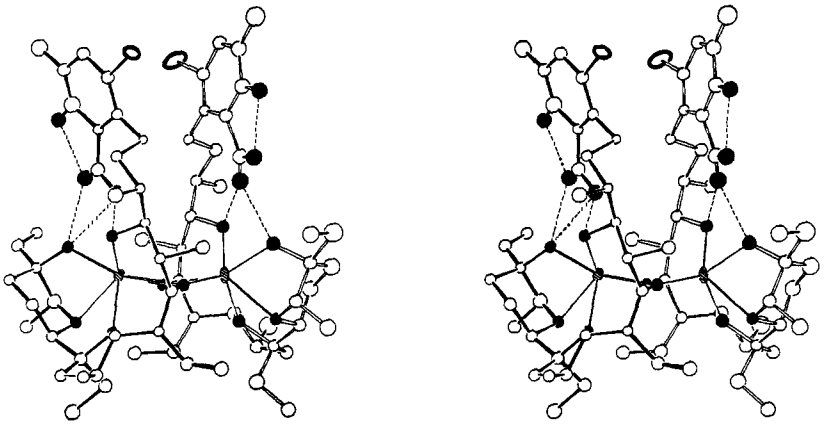

Figure 2. Stereoscopic view of the "head" to "head" structure in crystal modification II.

Table I. Crystal Data for Two Modifications of the Sodium Salt of 5-Br-X-537A

| | I | II |
|---|---|---|
| Formula | $Na_2(C_{34}H_{52}O_8Br)_2$ | |
| $M$ | 1383.4 | |
| System | orthorhombic | |
| $a$ (Å) | 16.92 (2) | 20.67 (1) |
| $b$ (Å) | 23.90 (3) | 16.05 (1) |
| $c$ (Å) | 18.55 (1) | 42.39 (1) |
| $V$ ($cm^3 \times 10^{-24}$) | 7501 | 14,064 |
| $Z$ | 4 | 8 |
| Space Group | $P2_12_12_1$ | $C222_1$ |
| No. of obsd reflections | 1681 | 3486 |
| $R$ factor | 0.107 | 0.127 |

"tail" and form II is "head" to "head." Neither dimer has crystallographic symmetry. The conformations of all four crystallographically independent X-537A molecules in the two dimers are very closely similar, and similar to those found in earlier work.[4-7] In each complex, the $Na^+$ ion is complexed ($Na^+ \cdots O$ distances of 2.28–2.77 Å) by five oxygen atoms (O15, O20, O31, O33, and O40) from one anion; in form I the resulting "basket" of oxygen atoms is capped by O26 from the other anion and in form II it is capped by O33 from the other anion. As these two dimers crystallized from solvents of different polarity, a solution nmr study was undertaken to probe the relevance of these structures to the solution environment.

The 220-MHz pmr spectra of **2** were obtained in $CDCl_3$, acetone-$d_6$, and three acetone–$CDCl_3$ mixtures of intermediate composition. Decoupling experiments at 100 MHz aided the assignments. Chemical shifts (parts per million from internal TMS) of resolved peaks, multiplicities, and coupling constants (in hertz), followed by assignments where possible, are given below for **2** in $CDCl_3$ (~30 mg/ml 28°): 0.58 (t, 6.8 ± 0.4 Hz); 0.80 (t, 6.8 ± 0.4); 0.86 (d, 5.9 ± 0.4); 0.97 (d, 7.0 ± 0.5) C32; 0.98 (t, 7.0 ± 0.5); 1.00 (d, 7.0 ± 0.5); 1.08 (d, 6.8 ± 0.4) C39; 2.19 (s) C29; 2.57 (d (brd), 11.0 ± 0.5)[8] C13; 2.86 (dq, 10.0 ± 0.8, 7.0 ± 0.5) C11; 3.45 (d (brd), 11.5 ± 0.5)[8] C19[9]; 3.68 (d (brd), 10.0 ± 0.5)[8] C14[9]; 3.93 (q, 7.0 ± 0.4) C21; 4.57 (d (brd), 10.5 ± 0.5)[8] C10; 7.25 (s) C4. On going from $CDCl_3$ to acetone several peaks were seen to shift by as much as 0.3 ppm. Chemical shift changes of all the peaks generally followed the same monotonic (but nonlinear) trend with molal solvent composition. Peaks assigned to C4, C11, C13, and the peak at $\delta$ 0.80 in $CDCl_3$ showed somewhat more complicated behavior. Over the solvent range no greater broadening was seen for the resonances with largest chemical shifts than for those which shifted the least, indicating either that only one conformation of the antibiotic is present in each intermediate solvent or that a limited number of species interconvert on a time scale short compared with the

(8) Peaks contain unresolved multiplets. Line widths (in Hz) at half height are: C13, 6.0; C19, 5.7; C14, 3.5; C10, 5.5.

(9) Assignments may be reversed.

chemical shift difference (exchange lifetime $\ll 3 \times 10^{-3}$ sec). The latter possibility is more likely (*vide infra*).

Within an uncertainty of *ca.* 0.5 Hz no solvent-dependent differences in vicinal coupling constants (or in line widths of unresolved multiplets) were detected for any resolved peaks including those for the backbone protons of C10, C11, and C13 or those for the cyclic ether ring protons on C14 and C19. Thus large conformational changes in much of the backbone or in the rings do not occur although the data do not exclude minor adjustments ($\lesssim 10°$) of the dihedral angles. Furthermore, the coupling constants in $CDCl_3$ and in acetone are all within $\sim$1 Hz of those estimated[10] on the basis of the torsion angles found in crystal modification I.

In contrast to the lack of variation of coupling constants with solvent, marked changes in the chemical shifts occur. Of particular interest are changes in peaks due to the methyl protons on the ethyl side chains since these resonances should be relatively insensitive to the changes in solvent *per se* or to changes in electron density around possible ligands to metal ions. In fact, one of the methyl triplets changes from $\delta$ 0.58 in $CDCl_3$ to $\delta$ 0.83 in acetone-$d_6$, a difference of 0.25 ppm, while the triplets at $\delta$ 0.80 and $\delta$ 0.98 in $CDCl_3$ are found in acetone at $\delta$ 0.84 and $\delta$ 0.90, respectively. Data for the free acid of Br-X-537A are useful for an interpretation of these effects. (This derivative has yielded only one crystalline form from several solvents and contains a "head" to "head" dimer.[4]) In $CDCl_3$ the three methyl triplets are found at $\delta$ 0.81, 0.83, and 0.94 ppm, and in acetone at $\delta$ 0.84, 0.84, and 0.87 ppm. None of the resonances of the free acid changes by more than 0.07 ppm between solvents so it is unlikely that the 0.25 ppm change seen for one peak in the sodium salt is a direct result of solvent interactions. Anisotropy due to an aromatic ring current is the most probable cause of the large upfield shift observed in the less polar solvent.

A conformational change within the monomeric unit is one possibility for the difference in going from acetone to $CDCl_3$. However, placing any one of the ethyl group methyls above the aromatic ring and close enough to give a 0.25 ppm shift requires a fairly substantial rearrangement. Such a conformation would probably not bind sodium and would probably be manifest in significant changes for vicinal coupling constants for backbone resonances, changes which are not observed. The crystal structure data offer another, more plausible, explanation for the ring current-induced shift.

In the molecular structure (Figure 1) obtained from crystals grown in $CCl_4$ (modification I) none of the methyl groups would experience any appreciable upfield shift due to the aromatic ring of their own chain. However, the protons of methyl C37 would be shifted upfield $\sim$0.7 ppm[11] due to the aromatic ring of its partner in the head-to-tail dimer. We have tentatively assigned the triplet at $\delta$ 0.58 ppm in $CDCl_3$ to C37.[12] Osmotic pressure data on the $Na^+$ salt of 5-Br-X-537A are consistent with dimer formation in chloroform, whereas in 1:1 $CHCl_3$–isopropyl alcohol, monomer is suggested.[13]

The nmr data strongly suggest the presence in nonpolar solvents of a dimeric form of $Na^+$ salt of 5-Br-X-537A similar (but not quite identical) to that found in the X-ray study on the crystals obtained from $CCl_4$. The progression of the C37 chemical shift to lower field as the solvent polarity increases is probably due to a facile equilibrium between a head-to-tail dimer and either a dimeric species of quite different orientation or else a monomeric species. In any case the backbone conformation is not appreciably perturbed by the solvent change. It is significant to note that a dimeric structure has been found in all six crystal structures of derivatives of X-537A and their salts (present work and ref 4–7). Furthermore the torsion angles in the backbone chain for the 12 independent X-537A molecules or anions do not vary by more than $\pm 8°$.

We believe that our work emphasizes the great importance of dimeric structures for X-537A in nonpolar solvents and also the need to recognize a high degree of conformational integrity in this system, factors which apparently have not always been given due attention.[3]

**Acknowledgment.** This work was supported by NIH Grants GM 19336 (I. C. P.) and GM 18038 (P. G. S.). We thank Dr. J. W. Westley of Hoffmann-La Roche, Inc., for provision of samples and helpful discussion.

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## Effect of Pressure on the Competing [2 + 2] and [2 + 2 + 2] Cycloadditions of Tetrachlorobenzyne and Norbornadiene[1]

*Sir:*

It is a well-known fact that liquid phase reactions characterized by bond formation are greatly facilitated by the application of hydrostatic pressure and, conversely, that bond cleavage is strongly impeded.[2] In recent years we obtained indications that processes involving multiple bond changes are proportionately more sensitive.[3] Since then a number of applications have been reported; thus, Eckert has shown by means of high pressure experiments that the Diels–Alder reaction is a concerted one and that it is subject to attractive secondary orbital interactions when these are possible.[4] Stewart[5] has applied the criterion to the

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