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STEREOCHEMICAL STUDIES OF LASALOCID EPIMERS. ION-DRIVEN EPIMERIZATIONS.

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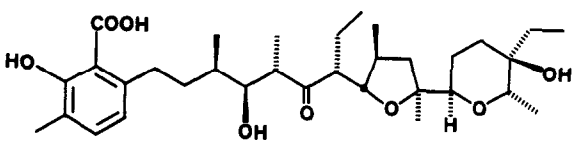
Abstract: Certain stereoisomers of the ionophore antibiotic lasalocid A can be epimerized to the natural configuration using metal ions which form particularly stable complexes with the natural antibiotic.

The most striking feature of the polyether antibiotics is their ability to form strong complexes with certain alkali and alkaline earth cations. For salts of lasalocid A (**1**),[1] one of the simplest polyethers, association constants can be as high as 10^6.



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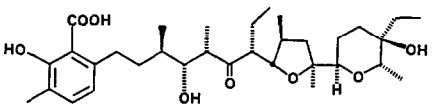
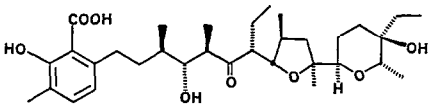
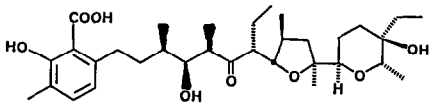
	K_a [2]
Li^+	48
Na^+	370
K^+	3,800
Ca^{++}	3,700
Ba^{++}	2,900,000

Many natural ionophores such as the polyethers are also of interest in that they are basically stereochemically complex acyclic chains of ligands and thus differ markedly from the synthetic ionophores such as 18-crown-6[3] which are typically macrocyclic ligating arrays. Both classes of ionophores are substantially better metal ion binders than simple linear polyethers (podands).[4] An important difference between the acyclic podands and macrocyclic corands is the greatly reduced conformational mobility of the latter in favor of conformations suitable for polydentate ion binding. The polyether antibiotics appear to achieve the same end by incorporation of rigidifying substructures such as 5- and 6-membered cyclic ethers and, most interestingly, particular arrays of chiral centers which destabilize undesired rotomers of acyclic bonds.

In a recent communication,[5] we presented a stereochemical assignment of the epimeric aldols of lasalocid A and described several highly stereoselective reactions whose control seemed to result from the overall structure of the ionophore. In this letter, we show that among the stereoisomeric aldols of lasalocid, the natural stereoisomer has the highest affinity for barium and that certain barium salts may be used to convert the low affinity epimers to the natural, high affinity aldol configuration.

Binding constants of the various lasalocid aldol stereoisomers shown below with barium bromide were measured by fluorescence in methanol as described previously[2] for lasalocid A itself and by UV difference spectroscopy. The binding constant we find for the natural configuration compares well with that reported (2.9×10^6) and is substantially larger than any of those found with the other aldol epimers.

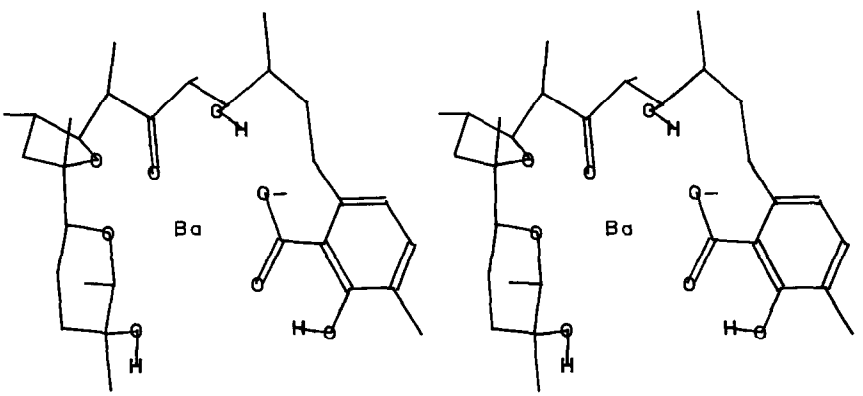
Stereoisomer		K_a
Natural (1)		2.1×10^6 (Fluorescence)
	2	$1.5\text{-}3.7 \times 10^4$ (Fluorescence) 3.9×10^4 (Difference UV)
	3	$0.9\text{-}2.1 \times 10^4$ (Fluorescence) 8.8×10^3 (Difference UV)
	4	No Fluorescence Change with Ba^{++} 7.8×10^3 (Difference UV)

Since the natural configuration binds barium 2-3 orders of magnitude more tightly than any of the epimers, it is likely that if a thermodynamic equilibrium between the barium salts of the epimers were established then it would favor the most stable complex, i.e. that with the natural configuration of lasalocid.[6] For such an equilibration, two of the epimers (2 and 3) would require hydroxyl epimerization (e.g. by retroaldol-realdol) and one (4) would require simple methyl epimerization (e.g. by enolization-ketonization). While basic solutions of barium or other metals led only to decomposition of the epimeric aldols, a stirred suspension of barium hydroxide octahydrate in hexane (25° C, 19 hours) converted the barium salt of epimer 4 to barium lasalocid in 63% yield. Epimers 2 and 3 also produced lasalocid but in much lower yields (6% and 5% respectively). Interestingly, the natural configuration of lasalocid was the only stereoisomer of the intact polyether detected in any of the equilibration mixtures with the remainder of the material being products of retroaldol and decomposition.

To assess the proposal that the natural configuration of lasalocid A is particularly suited for binding metal ions, we undertook a crude, hard sphere global search of the conformational space available to lasalocid system.[7] Using full circle 30° dihedral angle resolution for the low barrier C(sp2)-C(sp3) linkages (C7-C8,

C12-C13, C13-C14), 120° resolution for all C(sp3)-C(sp3) linkages (C8-C9, C9-C10, C10-C11, C11-C12, C14-C15, C18-C19) and +/- 30° for the C(sp2)-C(sp2) linkage of the barium carboxylate, 2.52 x 10^6 conformations were evaluated for nonbonded contacts (minimum 3.0 Ang for non-hydrogen 1,5-interactions and 2.0 Ang for all more remote interactions) and for barium ligation by carboxylate and the five aliphatic oxygens (maximum 4.0 Ang O-Ba distance).[8] The conformational space search described was completed in approximately 1 cpu minute on a VAX 11/780 using the internal coordinate conformer generator MULTIC as a submode of the interactive molecular modeling program MacroModel. With the stereochemistry of natural lasalocid, the search yielded only one structure and that structure was an idealized model of the conformer found in the x-ray structure of barium lasalocid.

Except for the trivial case of the C23 epimer, analogous searches on the other singly epimerized stereoisomers led to no structures which allowed ligation of the barium by the carboxylate and all 5 aliphatic oxygens without creating high energy nonbonded contacts. While we did not examine all of the possible diastereomers of lasalocid in this way, the doubly epimerized C10/C11, C11/C12, C10/C12, C14/C16, C15/C16 and C18/C19 isomers were also searched and, of these, only the C14/C16 isomer had conformers passing the nonbonded contact and oxygen ligation tests. One other isomer, the C10/C11/C12 triply epimerized material also yielded low energy, ligating conformers. While we have no evidence that this crude treatment can be used to predict tight binders of metals or other ligands, we believe that the simple analysis may serve to focus attention away from stereoisomers having little chance of forming strong complexes for steric reasons. Energy minimization of these potentially stable epimeric barium complexes yielded a C14/C16 structure having a main chain conformation which was essentially identical to that of the barium lasalocid x-ray structure and a more significantly modified C10/C11/C12 structure which is shown in stereo below.[9,10]



In conclusion, we have presented evidence that the polyether antibiotics use particular arrays of stereocenters to preorganize ligating atoms so that metal ions may be effectively bound. Experimentally, it was found that at least 3 unnatural epimers of lasalocid do not form strong complexes with barium. Computationally, it was shown that many of the unnatural epimers cannot use their standard complement of 6 oxygens to ligate barium and simultaneously avoid serious nonbonded interactions. While the computational model is quite crude, it is rapid and may provide a simple method with which to screen new structures for potential metal-binding properties.[11]

Notes and References:

1. J. Berger, A.I. Rachlin, W.E. Scott, L.H. Sternbach and M.W. Goldberg, J. Am. Chem. Soc., **73**, 5295 (1951).

2. H. Degani and H.L. Friedman, Biochemistry, **13**, 5022 (1974); B.C. Pressman, Fed. Proc., **32**, 1698 (1973).

3. H.K. Frensdorff, J. Am. Chem. Soc., **93**, 600 (1971).

4. E. Weber and F. Vogtle, Tetrahedron Lett., 2415 (1975).

5. W.C. Still, D. Kempf and P. Hauck, Tetrahedron Lett., **27**, 2727 (1986).

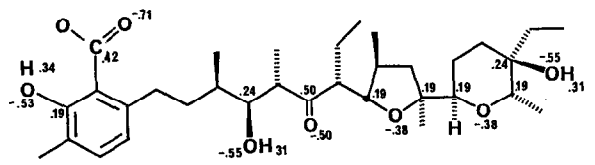
6. This proposal assumes that the relative energy differences of the epimers under consideration in the absence of barium would be comparatively small.

7. For purposes of the conformational analysis, the ethyl sidechains were replaced by methyl groups and the hydrogens on the hydroxyl groups were removed.

8. The oxygen-barium distances in the x-ray structure range from 2.7-3.1 Ang: S.M. Johnson, J. Herrin, S.J. Liu and I.C. Paul, J. Am. Chem. Soc., **92**, 4428 (1970).

9. Energies were minimized to a final gradient of 10^{-2} kj/Angstrom using the united atom AMBER force field using a distance-dependent dielectric with the additional parameters listed below. Although the field has not been optimized for structures of this type, least squares superimposition of the minimized barium complex and the most highly metal ligating lasalocid in the x-ray structure[8] of the dimeric barium complex gave an atomic deviation of 0.28 Angstroms.

Charges:



Benzoate C(sp2)-C(sp2):
Stretch: l = 1.50 A, k = 300
Torsion: V2/2 = 3.4 kcal/mole

Barium^{++}:
Rad = 2.0 Ang, Eps = 0.62

10. Previous molecular mechanics on ionophore complexes include: G. Wipff, P. Weiner and P. Kollman, J. Am. Chem. Soc., **104**, 3249 (1982); K. Hori, H. Yamada and T. Yamabe, Tetrahedron, **39**, 67 (1983); S. Lifson, C.E. Felder and A. Shanzer, J. Am. Chem. Soc., **105**, 3866 (1983); P.A. Kollman, G. Wipff and U.C. Singh, J. Am. Chem. Soc., **107**, 2212 (1985); R.A. Masut and J.N. Kushick, J. Comput. Chem., **6**, 148 (1985).

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