Table II. Effect of Ph_2SO Trapping on Et_2SO Formation

	$[Et_2SO] \times 10^3$ M		
$[Ph_2SO]$, M	$[Et_2S]$ = 0.020 M	$[Et_2S]$ = 0.050 M	$[Et_2S]$ = 0.10 M
0.010	2.93	3.45	3.38
0.020	3.29	4.00	3.56
0.025		4.11	4.25
0.050	4.33	5.49	5.27
0.100	6.18	6.45	7.44
0.150	7.40	7.64	7.71
0.175			8.41
0.200	7.83	8.03	

but not in benzene (no $[Et_2S]$ dependence of slope).

A modified scheme is obviously required to explain the behavior in benzene, where the amount of trapping depends on the concentration of the trap but not on that of diethyl sulfide; clearly, the two are not competing for a common intermediate in this solvent. A possible explanation for this behavior is that the primary intermediate can form sulfoxide without the intervention of a second sulfide molecule in this solvent (Scheme II). This explanation is also consistent with the otherwise very puzzling observation of Foote and Peters in benzene[2,3] (where the majority of the removal of singlet oxygen does not lead to product) that the fraction of quenching does not depend on sulfide concentration. This behavior was very difficult to reconcile with Scheme 1;[16] for an explanation of the observed kinetics, an implausible intervention of a second sulfide molecule in the quenching process was required (Scheme III). Under Scheme II, no sulfide concentration dependence of quenching is expected. From Scheme II, eq 3 and 4 follow:[14b]

$$\frac{[Et_2SO]}{[Ph_2SO_2]} = 1 + \frac{2k_{so}}{k_{pho}[Ph_2SO]} \tag{3}$$

$$[Ph_2SO_2]^{-1} = K^{-1}\left(1 + \frac{k_d}{k_s[Et_2S]}\right)\left(1 + \frac{k_{so}}{k_{pho}[Ph_2SO]}\right) \tag{4}$$

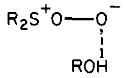
According to eq 3, the slope of the plot of Figure 1 should be independent of $[Et_2S]$, in agreement with the results in benzene. Also, since the term $k_d/k_s[Et_2S]$ in eq 4 can be neglected,[15] the slope and intercept of Figure 2 should be independent of $[Et_2S]$, as observed.

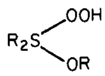
A prediction of Scheme II which was tested is that, in benzene, added Ph_2SO should increase the total amount of Et_2SO by suppressing the quenching step, since trapping and quenching are competitive. Table II shows that the expected relationship is observed.

Since Ph_2S traps the intermediate in benzene, and is only slightly less efficient than Et_2S (in methanol at least),[2,3] why does Et_2S not compete kinetically for the intermediate? The answer can be seen from Table I: trapping by 0.06 M Ph_2S in the reaction of 0.02 M Et_2S actually gives only 4.5×10^{-5} M Ph_2SO. Thus, the trapping by sulfides is too inefficient to compete with decay of the intermediate in benzene. Only the more efficient sulfoxides can compete enough to affect the kinetics.

Although several more complex reactions have been considered and are not ruled out, Scheme II is the simplest which can explain our observations. Foote and Peters determined the stoichiometry of the reaction to be two sulfides per singlet oxygen in methanol.[2,3] Peters[17] reported that the stoichiometry of the reaction was also 2:1 in benzene. This stoichiometry is not consistent with Scheme II. However, the stoichiometry cannot be determined easily under conditions where some 96% of the $^1O_2$ is quenched and only 4% gives product, as in benzene. A rationale for a change in stoichiometry is provided by the observation of Sawaki and Ogata[18] that phenol is a minor product of the reaction: inefficient attack on solvent benzene by the intermediate could result in the formation of phenol and sulfoxide. Other mechanisms for the reduction of the intermediate to sulfoxide without the intervention of a second sulfide are also possible.

The effect of protic solvents on the reaction is to dramatically favor product formation at the expense of quenching, with very little effect on the total removal rate of $^1O_2$.[2,3,10] We have repeatedly confirmed this observation of Foote and Peters, who suggested that stabilization of the intermediate by methanol was responsible for the effect. An alternate possibility, that addition of methanol to the intermediate occurs to give a peroxysulfurane **2**, similar to those proposed by Martin et al.,[11] seems less likely,





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since this intermediate would be expected to oxidize sulfides much more readily than sulfoxides.[18] From Table I, Ph_2SO is a better trap than Ph_2S, although less so than in methanol. These results parallel those of Sawaki and Ogata,[18] who report the intermediate to be nucleophilic in benzene but less so in methanol. Further work on this interesting system will be the subject of several papers in the near future.[19,20]

Acknowledgment. This work was supported by National Science Foundation Grant CHE77-21560.

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[16] Scheme I predicts that the fraction of quenching should increase as the Et_2S concentration decreases.

[17] Peters, J. W. *Dissertation*, University of California, Los Angeles, 1971.

[18] Sawaki, Y.; Ogata, Y. *J. Am. Chem. Soc.*, preceding paper in this issued. We thank Drs. Sawaki and Ogata for a prepublication copy of their manuscript.

[19] Taken in part from: Gu C.-L., Dissertation, University of California, Los Angeles, 1981. Kacher, M. L. Dissertation, University of California, Los Angeles, 1977.

[20] **Note Added in Proof**: A paper on sulfoxide trapping has just come to our attention: Cauzzo, G.; Gennari, G.; Da Re, F.; Curci, R. *Gazz. Chim. Ital.* **1979**, *109*, 541.

Observations on the Nature of Polylithium Organic Compounds and Their Rearrangements

Lawrence A. Shimp, John A. Morrison, John A. Gurak,
John W. Chinn, Jr., and Richard J. Lagow*

Department of Chemistry, University of Texas at Austin
Austin, Texas 78712

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Recently, there has been increasingly widespread theoretical interest in the structures and properties of polylithium organic compounds.[1-6] This has been coupled with and, in some instances, stimulated by a substantial amount of synthetic work.[7-10] The

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[1] Y. Apeloig, P. v. R. Schleyer, J. S. Binkley, and J. A. Pople, *J. Am. Chem. Soc.*, **98**, 4332 (1976).

[2] J. B. Collins, J. D. Dill, E. D. Jemmis, Y. Apeloig, P. v. R. Schleyer, R. Seeger, and J. A. Pople, *J. Am. Chem. Soc.*, **98**, 5419 (1976).

[3] (a) Y. Apeloig, P. v. R. Schleyer, J. S. Binkley, J. A. Pople, and W. A. Jorgensen, *Tetrahedron Lett.*, 3923 (1976); (b) E. D. Jemmis, D. Poppinger, P. v. R. Schleyer, and J. A. Pople, *J. Am. Chem. Soc.*, **99**, 5796 (1977); (c) G. Rauscher, T. Clark, D. Poppinger, and P. v. R. Schleyer, *Angew. Chem.*, **90**, 306 (1978); (d) E. D. Jemmis, J. Chandrasekhar, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **101**, 2848 (1979); (e) A. Kos, D. Poppinger, P. v. R. Schleyer, and W. Thiel, *Tetrahedron Lett.*, 2151 (1980).

[4] E. D. Jemmis, P. v. R. Schleyer, and J. A. Pople, *J. Organomet. Chem.*, **154**, 327 (1978).

[5] W. D. Laidig and H. F. Schaefer, *J. Am. Chem. Soc.*, **100**, 5972 (1978).

[6] W. D. Laidig and H. F. Schaefer, *J. Am. Chem. Soc.*, **101**, 7184 (1979).

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most striking and potentially significant predictions are that certain polylithium compounds will exhibit planar rather than tetrahedral carbon atoms,[2,5] that others will have electron-deficient, vapor-phase monomers involving bridging lithium sites,[3] and that those with substituted olefinic bonds will be skewed instead of planar[1,6] (e.g., the 1,1-dilithium substituted carbon plane would be orthogonal to the 2,2-substituted carbon plane in 1,1-dilithioethylene).

In view of this widespread interest, a worthwhile and significant question to ask is if such vapor-phase species exist or can be prepared. Upon initial inspection, it would appear that, unless the species were observed very quickly after being synthesized in the gas phase, no such monomeric gas-phase species could be produced. These conclusions follow from the fact that polylithium organic compounds are thermally stable only to 200–225 °C, and there is no observable vapor pressure to at least 650 °C. Therefore, polylithium compounds decompose or rearrange extensively long before they vaporize.

The polylithium organic compounds prepared in our laboratory appear to be three-dimensional, electron-deficient, polymeric networks which are held together by forces similar to those in species such as the methyllithium tetramer, the ethyllithium tetramer, etc.[11] Unfortunately, confirmation of the structural features of these compounds has been hampered by their extremely low solubility in inert solvents. Thus, obtaining useful solution ^{13}C NMR data or growing crystals from solution suitable for X-ray diffraction studies have not been successful so far, even though these compounds are sparingly soluble in cold THF, as evidenced by weak ^{7}Li NMR signals observed in such solutions and the subsequent recovery of the compounds from solution. However, at temperatures higher than about −30 °C, the polylithium compounds begin to react with the THF solvent. Further work in this area is being pursued vigorously.

It is clear from experimental work in our laboratory that there is a series of relative thermal stability of polylithium compounds ranging from perlithioalkanes, through the more unsaturated species, and culminating in the most stable lithiocarbon compound, lithium acetylide or lithium carbide (C_2Li_2). $(CLi_4)_m$[9] $(CH_2Li_2)_m$,[12] $(C_3Li_4)_m$,[7] and other polylithium compounds undergo rearrangement at 220 °C over a short period of time and undergo such rearrangements extremely rapidly if the temperature is increased. The following thermal stability series has been established from this work:

$$CLi_4 < C_2Li_4 < C_3Li_4 < C_2Li_2$$

We have chosen three examples of polylithium compounds to illustrate this system of thermal rearrangements and stability. Reactions of the following types have been observed:

$$CLi_4 \xrightarrow{\Delta} C_2Li_4 \xrightarrow{\Delta} C_3Li_4 \xrightarrow{\Delta} C_2Li_2 \qquad (1)$$

$$CH_2Li_2 \xrightarrow{\Delta} C_2Li_2 + C_3Li_4 \qquad (2)$$

$$C_3Li_4 \xrightarrow{\Delta} C_2Li_2 \qquad (3)$$

The byproduct of such reactions in the case of the perlithiated species is lithium, and in the case of dilithiomethane, the byproducts include lithium hydride. These rearrangement reactions do not necessarily go through each distinct stage if carried out very rapidly. The degree of shift toward the more stable compounds on the right side of the equation depends on the temperature and duration of the pyrolysis or rearrangement in the thermal environment. A large number of such reactions have been studied and observed, and several specific cases are listed in this communication to convey the essence of the rearrangements. Approximately 1-g samples were used in each pyrolysis experiment.

Tetralithiomethane

$$CLi_4 \xrightarrow[2\ \mathrm{min}]{225\ °C} CLi_4\ (60\%) + C_2Li_4\ (20\%) + C_3Li_4\ (20\%) \qquad (4)$$

$$CLi_4 \xrightarrow[8\ \mathrm{min}]{225\ °C} CLi_4\ (20\%) + C_2Li_4\ (30\%) + C_3Li_4\ (40\%) + C_2Li_2\ (10\%) \qquad (5)$$

$$CLi_4 \xrightarrow[10\ \mathrm{min}]{225\ °C} C_2Li_2\ (100\%) \qquad (6)$$

$$CLi_4 \xrightarrow[5\ \mathrm{min}]{500\ °C} C_2Li_2\ (100\%) \qquad (7)$$

Dilithiomethane

$$CH_2Li_2 \xrightarrow[6\ \mathrm{min}]{350\ °C} C_3Li_4\ (20\%) + C_2Li_2\ (80\%) \qquad (8)$$

$$CH_2Li_2 \xrightarrow[10\ \mathrm{min}]{400\ °C} C_2Li_2\ (99\%) \qquad (9)$$

C_3Li_4

$$C_3Li_4 \xrightarrow[3\ \mathrm{min}]{300\ °C} C_3Li_4\ (40\%) + C_2Li_2\ (60\%) \qquad (10)$$

$$C_3Li_4 \xrightarrow[10\ \mathrm{min}]{350\ °C} C_2Li_2\ (100\%) \qquad (11)$$

These rearrangements and the relative stability of such compounds clearly illustrate the reason why prior to the work of Ziegler and co-workers,[12] West and co-workers,[7,8] and Lagow and co-workers,[9,10] no simple polylithium or perlithium compounds were known. In the phase diagram of lithium and carbon, only the acetylide of stoichiometry C_2Li_2 has been observed. This is a direct consequence of the fact that carbon is not soluble in lithium below 650 °C. Lithium acetylide must be looked upon as displaying the same stability role in lithiocarbon systems as CF_4 in fluorocarbon systems and CO_2 in oxocarbon systems.

The reported reactions were characterized by hydrolysis with D_2O after the temperature of the reactant had been raised for the specified period of time, followed by gas chromatographic separation of the deuterated compounds on a phenyl isocyanate column, and characterization with both low- and high-resolution mass spectroscopy. The lithiated species were also derivatized with chlorotrimethylsilane. An interesting observation which can

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(7) (a) R. West, P. A. Carney, and I. C. Mineo, *J. Am. Chem. Soc.*, **87**, 3788 (1965); (b) R. West and P. C. Jones, *ibid.*, **91**, 6156 (1969).

(8) (a) R. West and P. C. Jones, *J. Am. Chem. Soc.*, **90**, 2656 (1968); (b) G. A. Gornowicz and R. West, *ibid.*, **93**, 1714, 1720 (1971); (c) T. L. Chwang and R. West, *ibid.*, **95**, 3324 (1973); (d) W. Priester, R. West, and T. L. Chwang, *ibid.*, **98**, 8413 (1976); (e) W. Priester and R. West, *ibid.*, **98**, 8426 (1976).

(9) (a) C. Chung and R. J. Lagow, *J. Chem. Soc., Chem. Commun.*, 1078 (1972); (b) L. A. Shimp and R. J. Lagow, *J. Am. Chem. Soc.*, **95**, 1343 (1973).

(10) (a) L. G. Sneddon and R. J. Lagow, *J. Chem. Soc., Chem. Commun.*, 302 (1975); (b) J. A. Morrison, C. Chung, and R. J. Lagow, *J. Am. Chem. Soc.*, **97**, 5015 (1975); (c) J. A. Morrison and R. J. Lagow, *Inorg. Chem.*, **16**, 2972 (1977); (d) L. A. Shimp, C. Chung, and R. J. Lagow, *Inorg. Chim. Acta*, **29**, 77 (1978); (e) K. M. Abraham and R. J. Lagow, *Tetrahedron Lett.*, 211 (1979); (f) L. A. Shimp and R. J. Lagow, *J. Am. Chem. Soc.*, **101**, 2214 (1979); (g) L. A. Shimp and R. J. Lagow, *J. Org. Chem.*, **44**, 2311 (1979).

(11) (a) T. L. Brown and M. T. Rogers, *J. Am. Chem. Soc.*, **79**, 1859 (1957); (b) R. West and W. Glaze, *ibid.*, **83**, 3580 (1961); (c) J. Berkowitz, D. A. Bafus, and T. L. Brown, *J. Phys. Chem.*, **65**, 1380 (1961); (d) T. L. Brown, D. W. Dickerhoof, and D. A. Bafus, *J. Am. Chem. Soc.*, **84**, 1371 (1962); (e) M. Weiner, G. Vogel, and R. West, *Inorg. Chem.*, **1**, 654 (1962); (f) M. A. Weiner and R. West, *J. Am. Chem. Soc.*, **85**, 485 (1963); (g) H. Dietrich, *Acta Crystallogr.*, **16**, 681 (1963); (h) E. Weiss and E. A. C. Lucken, *J. Organomet. Chem.*, **2**, 197 (1964); (i) T. L. Brown and J. A. Ladd, *ibid.*, **2**, 373 (1964); (j) T. L. Brown, *Adv. Organomet. Chem.*, **3**, 365 (1965); (k) L. M. Seitz and T. L. Brown, *J. Am. Chem. Soc.*, **88**, 2174 (1966); (l) L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *ibid.*, **90**, 3244 (1968); (m) T. L. Brown, L. M. Seitz, and B. Y. Kimura, *ibid.*, **90**, 3245 (1968); (n) L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *ibid.*, **91**, 1057 (1969); (o) M. Y. Darensbourg, B. Y. Kimura, G. E. Hartwell, and T. L. Brown, *ibid.*, **92**, 1236 (1970); (p) H. L. Lewis and T. L. Brown, *ibid.*, **92**, 4664 (1970); (q) E. Weiss and G. Hencken, *J. Organomet. Chem.*, **21**, 265 (1970); (r) T. L. Brown, *Pure Appl. Chem.*, **23**, 447 (1970); (s) W. M. Scovell, B. Y. Kimura, and T. G. Spiro, *J. Coord. Chem.*, **1**, 107 (1971); (t) W. E. Beckenbaugh, J. M. Geckle, and G. Fraenkel, *Chem. Scr.*, **13**, 150 (1978–1979); (u) G. Fraenkel, M. Henrichs, J. M. Hewitt, B. M. Su, and M. J. Geckle, *J. Am. Chem. Soc.*, **102**, 3345 (1980).

(12) K. Ziegler, N. Nagel, and P. Patheiger, *Z. Anorg. Allg. Chem.*, **282**, 345 (1955).

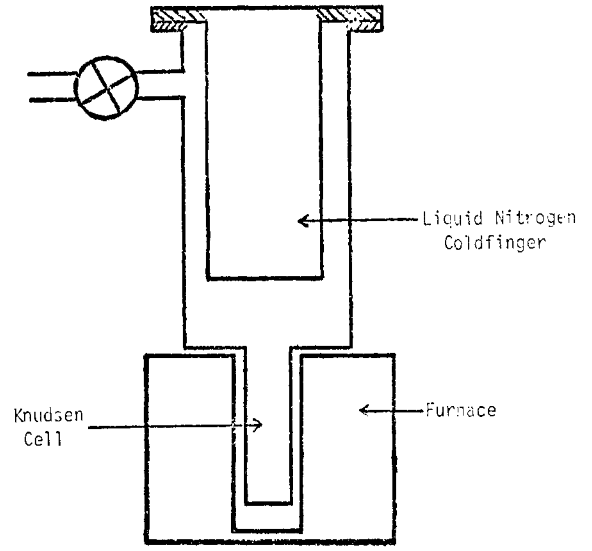

Figure 1. Improved reactor.

be made from these experiments is that the species (C$_3$Li$_4$)$_n$, which was first prepared by Robert West and co-workers from the reaction of butyllithium and propyne,[7] is an exceedingly stable polylithium compound, with a stability just below that of lithium carbide.

These results illustrate that, although it will be experimentally difficult to do so, there is hope for structurally characterizing gas-phase polylithium organic species; and, perhaps, it may involve techniques such as crossed-beam laser spectroscopy or matrix methods. We have discovered recently that flash vacuum heating of such compounds can result in vapor transport across a 10-cm path with no more than 10% decomposition. For example, if approximately 1 g of dilithiomethane is placed in the lower chamber of a reactor like the one shown in Figure 1 and heated very rapidly (from room temperature to approximately 1500 °C in less than 3 s), dilithiomethane is recovered 90% intact:

$$CH_2Li_2 \xrightarrow[2\ \mathrm{s}]{1500\ ^\circ\mathrm{C}} CH_2Li_2\ (90\%) + C_3Li_4\ (2\%) + C_2Li_2\ (8\%)$$

Such extremely fast flash heating can be effected by heating the Inconel metal Knudsen cell (see Figure 1) with induction coils, using a 30 kW, 300-kHz radio frequency generator. Experiments of this type made it clear that it is possible to obtain short-lived, high-temperature mass spectra, and such experiments are being conducted in our laboratory. These spectra will help elucidate and identify at least the stoichiometries of the gas-phase species actually observed for polylithium compounds. Thus far, the studies have shown that these electron-deficient, three-dimensional polymers produce not only monomers in the gas phase but also small polymeric clusters ranging in size from dimers to octamers; in many cases, the polymeric species are more abundant than the monomeric ones.[13] Specifically, the vapor species observed for (CH$_2$Li$_2$)$_n$ include (CH$_2$Li$_2$)$_n^+$ (n = 1–6), those for (CLi$_4$)$_n$ include (CLi$_4$)$_n^+$ (n = 1–5), and those for (C$_3$Li$_4$)$_n$ include (C$_3$Li$_4$)$_n^+$ (n = 1–3).

In light of such observations, Schleyer and co-workers have begun focusing more intensive ab initio calculational efforts toward the prediction of the structures and stabilities of dimers and other polymers in the gas phase. Their calculations have indicated that many dimers and trimers are exceedingly stable.[4,14]

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(13) J. W. Chinn, Jr., J. A. Gurak, and R. J. Lagow, to be published.
(14) P. v. R. Schleyer, Private communication.

Biosynthesis of Macrolides. 5. Regiochemistry of the Labeling of Lasalocid A by ^{13}C,^{18}O-Labeled Precursors

C. Richard Hutchinson[*,†] and Mary M. Sherman

School of Pharmacy, University of Wisconsin
Madison, Wisconsin 53706

John C. Vederas and Thomas T. Nakashima

Department of Chemistry, University of Alberta
Edmonton, Alberta, Canada T6G 2G2

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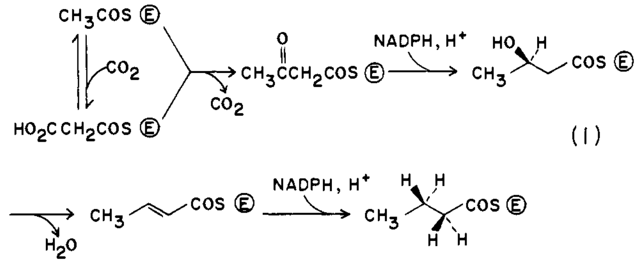
Macrolide and polyether antibiotics as well as fatty acids are believed to be constructed by similar or identical processes in eukaryotic organisms.[1] It is known that fatty acid biosynthesis occurs by the condensation of enzyme-bound acetate and malonate through a repetitive sequence of four stereospecific enzymatically catalyzed reactions (eq 1), within a large, multienzyme complex, and without the intervention of non-enzyme-bound intermediates.[2] It has therefore been presumed that the archetypal macrolide antibiotic erythromycin A (**1**) and the polyether ionophore antibiotic lasalocid A (**2**) are assembled in the same way from either acetate, propionate, or butyrate via their respective malonate analogues.[3] However, if this were true, corresponding chiral centers in the C$_2$–C$_4$ subunits of **1** and **2** should have the same absolute configurations. The stereochemistry of **1** and **2**, as well as that of their simplest putative precursors, **3**[3] and **4**,[6b] appears to be inconsistent with such a simplistic concept for their biogenesis because the absolute configuration of secondary alcohol and methine carbons derived from separate precursor molecules varies irregularly.[4] Consequently, either the enzymology of macrolide and polyether antibiotic biosynthesis is much more complex than suggested by the analogy to fatty acid biosynthesis or the stereocontrol over the formation of these antibiotics occurs subsequent to the carbon chain elongation process.



(1)

[†] Research Career Awardee of the National Cancer Institute (CA 00253), 1976–1981.

(1) (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Omura, S.; Nakagawa, A. *J. Antibiot.* **1975**, *28*, 401. (c) Queener, S. W.; Sebek, O. K.; Vezina, C. *Annu. Rev. Microbiol.* **1978**, *32*, 593.

(2) (a) Volpe, J. J.; Vagelos, P. R. *Physiol. Rev.* **1976**, *56*, 339. (b) Bloch, K.; Vance, D. *Annu. Rev. Biochem.* **1977**, *46*, 263. (c) Wakil, S. J.; Bressler, R. *J. Biol. Chem.* **1962**, *237*, 687. (d) Sedgwick, B.; Cornforth, J. W.; French, S. J.; Gray, R. T.; Kelstrup, E.; Willadsen, P. *Eur. J. Biochem.* **1977**, *75*, 481. (e) Seyama, Y.; Kasama, T.; Yamakawa, T.; Kawaguchi, A.; Okuda, S. *J. Biochem. (Tokyo)* **1977**, *81*, 1167; **1977**, *82*, 1325. (f) Sedgwick, B.; Morris, C.; French, S. J. *J. Chem. Soc., Chem. Commun.* **1978**, 193. (g) Sedgwick, B.; Morris, C. *Ibid.* **1980**, 96. (h) Kawaguchi, A.; Yoshimura, T.; Saito, K.; Seyama, Y.; Kasama, T.; Yamakawa, T.; Okuda, S. *J. Biochem. (Tokyo)* **1980**, *88*, 1. (i) White, R. H. *Biochemistry* **1980**, *19*, 9.

(3) (a) Hung, P. P.; Marks, C. L.; Tardrew, P. L. *J. Biol. Chem.* **1965**, *240*, 1322. (b) Martin, J. R.; Rosenbrook, W. *Biochemistry* **1967**, *6*, 435.

(4) W. D. Celmer (Celmer, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 1801. Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413) has noted that there is a remarkable stereochemical homogeneity among the different classes of macrolide antibiotics produced by bacteria. This fact suggests the occurrence of evolutionary consistency during the development and maintenance of the pertinent enzymatic systems.

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