Table I. Equilibrium Constants (K_{eq}) and Free Energies of Isomerization (ΔF_{isom}) for the Equilibrium **1** ⇌ **2**

Temp, °C	K_{eq}	ΔF_{isom}, kcal/mole
0.0	7.45	−1.09 ± 0.03
25.0	6.26	−1.09 ± 0.03
50.0	5.48	−1.09 ± 0.03

position and were analyzed by gas chromatography[17] using a 4-m column of Carbowax 1000 on 70–80 mesh silanized Chromosorb P.

The conformation of **2** is such that the cyclopropyl ring is fixed in its minimum energy conformation with respect to the double bond, thus effecting a maximum contribution due to delocalization. From the above data, this isomer has (from a least-squares evaluation) a lower heat of formation [$\Delta H_{f,298}$(l)] of 1.08 ± 0.07 kcal/mole in LDMA–HMPA solution than does the nonconjugated isomer **1**.

The important consideration is the amount of stabilization *in terms of chemical binding energy* which is a consequence of the structural feature of conjugation in **2** relative to **1**. In order to determine this, other terms contributing to $\Delta H_{f,298}$(l) must be estimated and eliminated. These include terms due to conformational, intermolecular interaction, kinetic, and zero-point energy differences.

Differences between structurally similar compounds due to the last three factors are generally considered to be minimal.[18,19] The one conformational energy term for which a correction may be needed is due to differences in torsional strain. We estimate that **2** possesses, if any, not more than *ca.* 0.2 kcal/mole more torsional strain than **1**.[20] Thus the chemical binding energy of **2** is estimated to be 1.1 to 1.3 kcal/mole greater than that of **1**.

Although it is difficult to estimate the contribution of delocalization to the above corrected empirical resonance energy, these results are relevant to the problem of the delocalization energy of 1,3-butadiene. Our approach is to arbitrarily ascribe all of the corrected empirical resonance energy of the vinylcyclopropyl system to hybridization effects and to correct for estimated hybridization differences between this system and 1,3-butadiene, thereby estimating the *maximum* contribution of hybridization effects in the diene system. Taking the exocyclic orbitals of the cyclopropyl ring to have 31% s character[21] and using "hybridization ratios"[2a] calculated from the bond angles in cyclohexane,[22] 1,3-butadiene,[23] propene,[24] and butane,[25] one can, using the bond energy scheme of Cox[26] (which assumes that all carbon–carbon single bond energy differences are due to hybridization), assign a *maximum* contribution of 1.7 kcal/mole to the empirical resonance energy of 1,3-butadiene due to hybridization effects. This, therefore, indicates that delocalization contributes a *minimum* of 1.9 kcal/mole to the corrected empirical resonance energy (3.6 kcal/mole)[19] of 1,3-butadiene.[27] This figure will be larger by at least the amount which delocalization contributes to the empirical resonance energy of the vinylcyclopropyl system.

Acknowledgment. We are pleased to acknowledge the support of this work by the Maryland General Research Board and the Petroleum Research Fund of the American Chemical Society.

(17) Relative peak areas were calibrated using known mixtures.

(18) (a) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworth & Co. (Publishers) Ltd., London, 1958, p 104; (b) G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p 76.

(19) Correction for these terms *reduces* the empirical resonance energy of 1,3-butadiene[5] by less than 10% (to 3.6 kcal/mole). This latter quantity is ΔH_0(g) minus the zero-point energy contributions. The zero-point energies of butane and 1-butene [T. L. Cottrell, *J. Chem. Soc.*, 1448 (1948)] were used along with the zero-point energy for 1,3-butadiene calculated from the frequency assignments reported by R. K. Harris, *Spectrochim. Acta*, 20, 1129 (1964).

(20) The minimum torsional strains were carefully estimated with the use of Dreiding models. The vinylcyclopropyl barrier was taken to be 2.5 kcal/mole[9] and the interorbital angle for cyclopropane was taken to be 100° [C. J. Fritchie, Jr., *Acta Cryst.*, 20, 27 (1966)].

(21) This value corresponds to ∠CCC = 116.7° (in the cyclohexene ring), which is intermediate between ∠HCH = 120° for cyclopropane [H. H. Gunthard, R. C. Lord, and T. K. McCubbin, Jr., *J. Chem. Phys.*, 25, 768 (1956)] and ∠CCC = 111.55° in cyclohexane.[22] It is weighted toward the cyclopropane value because of the flexibility of the cyclohexene part of the spiran system and is probably a low estimate.

(22) M. Davis and O. Hassel, *Acta Chem. Scand.*, 12, 1221 (1958).

(23) A. Almenningen, O. Bastiansen, and M. Traetteberg, *ibid.*, 12, 1221 (1958).

(24) D. R. Lide, Jr., and D. Christensen, *J. Chem. Phys.*, 35, 1372 (1961).

(25) R. A. Bonham and L. S. Bartell, *J. Am. Chem. Soc.*, 81, 3491 (1959).

(26) J. D. Cox, *Tetrahedron*, 19, 1175 (1963); 18, 1337 (1962). The hybridization values used by Cox were modified to correspond to the bond angles in the model compounds.

(27) Recent calculations suggest a significant delocalization energy for 1,3-butadiene [0.2047 ev: M. J. S. Dewar and G. J. Gleicher, *J. Am. Chem. Soc.*, 87, 692 (1965)], although this value is thought to be too high: M. J. S. Dewar, private communication.

Stuart W. Staley
Department of Chemistry, University of Maryland
College Park, Maryland 20740
Received December 21, 1966

Inversion during the Addition of Amino Acids to the D-*cis*-α-[Co(L,L-α,α′-dimethyltrien)Cl$_2$]$^+$ Ion

Sir:

An important approach to elucidating reaction mechanisms is through the study of stereochemistry. J. C. Bailar and his co-workers have pioneered the use of this approach in inorganic chemistry through their work with optically active cobalt–polyamine complexes.

In work with the optically active *cis*-dichlorobis(ethylenediamine)cobalt(III) cation, it was shown that inversion could be caused under certain conditions by displacing the chloride ions with either carbonate or ammine.[1] As was pointed out, the amount of inversion during carbonate substitution was shown to be dependent on several variables. These were concentration of the complex, concentration of the silver ion added, concentration of the carbonate ion present, ratio of hydroxide ion concentration to complex ion concentration, and the reaction sequence. Further, with ammine substitution in liquid ammonia, inversion was noted to be temperature dependent.[2,3] No studies have been reported in which the substituting ligand is an amino acid or an optically active amino acid.

Bailar and McReynolds[4] studied substitutional inversion with the D-*cis*-dichlorobis(*l*-propylenediamine)-cobalt(III) ion. However, it is impossible to conclude from their work to what extent the optical activity of

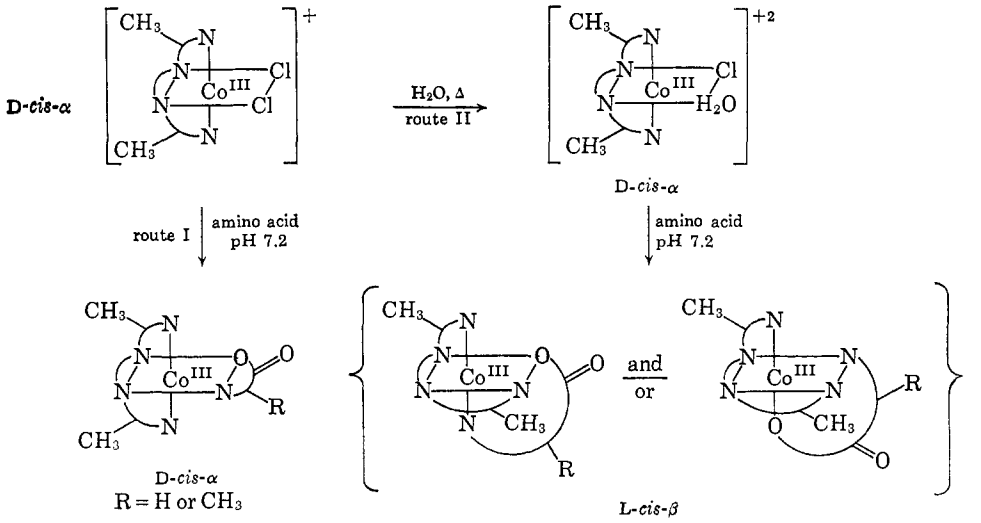
(1) L. J. Boucher, E. Kyuno, and J. C. Bailar, Jr., *J. Am. Chem. Soc.*, 86, 3656 (1964), and references therein.

(2) J. C. Bailar, Jr., J. H. Haslam, and E. N. Jones, *ibid.*, 58, 2226 (1936).

(3) R. D. Archer and J. C. Bailar, Jr., *ibid.*, 83, 812 (1961).

(4) J. C. Bailar, Jr., and J. P. McReynolds, *ibid.*, 61, 3199 (1939).

Scheme I



the diamines affects the mechanisms of isomerization and racemization.

In a further investigation of the reactions of the D-*cis*-*c*-[Co(L,L-α,α′-dimethyltrien)Cl_2]$^+$ ion,[5] it was observ d that glycine, D-alanine, and L-alanine could be added to the complex. The predominant product was formed either with or without inversion of configuration depending upon reaction conditions. The additions were made in essentially neutral solution, [OH] = 1.59×10^{-7} *M*, and the products isolated by fractional crystallization.

The results of these studies are important to the understanding of inorganic inversion–isomerization processes for the following reasons: (1) some of the displacing anions used were optically active and contained two different types of coordinating atoms; (2) the reactions took place in essentially neutral aqueous solution; and (3) the reacting complex contained an optically pure tetradentate amine in which the optical centers have been shown to play an important role in configurational stability.[5,6]

Scheme I illustrates the preparative conditions and resulting predominant isomeric products (representing 70–95% of the yield). In route I preparations, an aqueous solution of the complex and the amino acid was prepared. This solution was heated for several minutes on a steam bath while maintaining the pH at 7.2. The reaction occurred rapidly with the original purple solution becoming red-orange in 5 min.

In route II preparations, the aqueous solution of the complex was heated on the steam bath for several minutes to complete the aquation to the aquo–chloro compound before the amino acid was added and the pH adjusted to 7.2. Monoaquation was shown to occur with full retention of configuration as indicated by the slow appearance of a methyl doublet at τ 8.55 and concurrent disappearance of the dichloro's methyl doublet at τ 8.60 (for both, J_{H-CH_3} = 6.5 cps) in the nmr spectrum. Also, comparisons between the ORD spectra of the dichloride and the diaquo and the aquation products support the structural assignment of the aquo–chloro complex. The inverted product (L-*cis*-β) has a methyl multiplet in the nmr spectrum and a Cotton effect with the opposite sign in the ORD curve.[6,7]

(5) R. G. Asperger and C. F. Liu, *Inorg. Chem.*, **4**, 1395 (1965).
(6) R. G. Asperger, Dissertation, The University of Michigan, 1965.

In this way, the mono aquation of the stereoselective ion D-*cis*-α-[Co(L,L-α,α′-dimethyltrien)Cl_2]$^+$ is similar to the monoaquation deduced for the ion *cis*-α-[Co(trien)Cl_2]$^+$.[8] It is also similar to the monohydrolysis assumed for the ion *cis*-α-[Co(trien)Cl_2]$^+$.[9]

The individual reactions were repeated several times, and no evidence for racemization of the complex ion was noted, *i.e.*, D-*cis*-α → L-*cis*-α. The inversion was stereospecific, going from D-*cis*-α to L-*cis*-β. The optical activity of the substituting amino acid was not important in determining the amount of inverted product obtained. Only the reaction sequence appeared to control the amount of inversion noted.

The large yield of the thermodynamically less stable L-*cis*-β isomer[6,7] indicates that the route II reactions are kinetically controlled. In this respect, inversions noted during route II are similar to the observations of Bailar and McReynolds[4] for the reaction D-*cis*-[Co(*l*-pn)$_2$$Cl_2$]$^+$ → D- or L-*cis*-[Co(*l*-pn)$_2$$CO_3$]$^+$, where the D isomer (the more stable configuration for the *l*-pn complexes)[10-13] was the product of the slow reaction.

The presence of the ethylene bridge connecting the two L-propylenediamine moieties does not seem to be influential in the course of the reaction. This is surprising since the bridge is important in determining the isomer yields for the complex ion [Co(L,L-α,α′-dimethyltrien)Cl_2]$^+$: D-*cis*-α >>> L-*cis*-β >> *trans*; no L-*cis*-α or D-*cis*-β.[5]

The fact that inverted products predominate in route II products points to a mechanism involving inversion at some point after the first chloride has been aquated. From these studies, however, it is impossible to tell if the amine or carboxylate group of the amino acid attacks the intermediate coordination complex first. Also it is impossible to tell what coordination site is first involved. The fact that some product with configuration retention is isolated as a minor product

(7) R. G. Asperger and C. F. Liu, *J. Am. Chem. Soc.*, **89**, 708 (1967).
(8) A. M. Sargeson and G. H. Searle, *Nature*, **200**, 356 (1963).
(9) E. Kyuno, L. J. Boucher, and J. C. Bailar, Jr., *J. Am. Chem. Soc.*, **87**, 4458 (1965).
(10) F. P. Dwyer, A. M. Sargeson, and L. B. James, *J. Am. Chem. Soc.*, **86**, 590 (1964).
(11) F. P. Dwyer, T. E. McDermott, and A. M Sargeson, *ibid.*, **85**, 2913 (1963).
(12) T. E. McDermott and A. M. Sargeson, *Australian J. Chem.*, **16**, 334 (1963).
(13) E. J. Corey and J. C. Bailar, Jr., *J. Am. Chem. Soc.*, **81**, 2620 (1959).

in route II preparations indicates that at least two competing reactions are involved.

The products from these reactions were isolated by fractional crystallization and identified by elemental analyses and by comparing their ORD and nmr spectra with those reported earlier.[7] The ORD spectra were measured on a Cary 60 ORD using concentrations in the range of 15–20 mg of sample for 10 ml of H_2O and a 1.0-cm path length in the spectral range 600–380 mμ. A tenfold dilution and a path length of 0.10 cm were used in the range 300–185 mμ. Nmr spectra were taken on a Varian A-60[14] at a concentration of about 0.005 g/0.1 cc of D_2O at the probe ambient temperature (≈35°). Scans were taken after the solutions had stood at room temperature for 1–2 hr, and the spectra showed that all exchangeable hydrogens were lost. An external standard of sodium tetramethylsilane was used.

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(14) The solutions were prepared in a microcell; scans were on the "Dog" mode of the time-averaging attachment by the Dow Chemical Co., Midland, Mich.

Robert G. Asperger
Edgar C. Britton Research Laboratory
The Dow Chemical Company, Midland, Michigan
Chui Fan Liu
Department of Chemistry, University of Illinois
Chicago, Illinois 60680
Received August 5, 1966

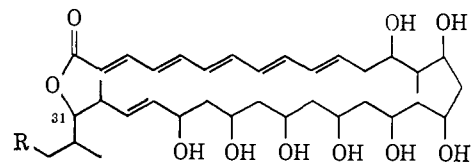
The Mycoticins, Polyene Macrolides from *Streptomyces ruber*[1]

Sir:

Mycoticin is a yellow, crystalline neutral metabolite of *Streptomyces ruber* exhibiting notable activity against pathogenic fungi. Its isolation was first reported in 1954 by Burke, *et al.*,[2] who suggested the formula $C_{18}H_{30}O_5$ and provided a brief chemical and physical characterization.

We wish to summarize here the results of a structural investigation on this pigment showing it to be a mixture of two polyene, polyhydroxy macrocyclic lactones,[3] mycoticin A, $C_{36}H_{58}O_{10}$ (Ia), and the homolog, mycoticin B, $C_{37}H_{60}O_{10}$ (Ib).

After repeated recrystallization from methanol, mycoticin[4] is obtained as fine yellow needles, mp 221–222°, which rapidly decompose in air and light;[5]



I a, R = H
b, R = CH_3

$[\alpha]^{22}D$ +63.4° (0.48%, dioxane); infrared peaks (KBr) at 3400 (broad OH), 1695 (C=O), 1610 (C=C), 1570 (conjugated C=C), and 1010 cm^{-1}. Mycoticin shows between three and four C-methyl groups in Kuhn–Roth analysis and gives negative Zeisel and ferric chloride tests and also negative reactions for aldehyde or ketone, vicinal hydroxyl groups (periodate), and primary alcohol (trityl chloride in pyridine). Presence of a pentaene system conjugated to a carbonyl group is shown by the ultraviolet absorption spectrum, exhibiting broad bands at λ_{max}^{EtOH} 262 ($E_{1\,cm}^{1\%}$ 79) and 364 mμ ($E_{1\,cm}^{1\%}$ 948), in good agreement with the absorption expected for conjugated ester–pentaene chromophores.[6] Likewise, reduction of the carbonyl group in mycoticin with lithium aluminum hydride yields a product showing a pattern of peaks at 303, 317, 328, and 349 mμ which is characteristic of conjugated pentaene systems such as dodeca-2,4,6,8-pentaene[7] and tetrahydrocicutol.[8] Further confirmation of the location of the double bond system adjacent to the carbonyl group is found in the results of the sequence: ozonolysis of mycoticin, catalytic hydrogenation, and then saponification, whereby glycolic acid is formed.

The presence of an isolated double bond in the molecule is indicated by the consumption of a sixth mole of hydrogen on catalytic hydrogenation to give dodecahydromycoticin,[9] mp 138.2–138.8°, showing a carbonyl peak in the infrared at 1725 cm^{-1}. Dodecahydromycoticin is unusually resistant toward hydrolysis, requiring long refluxing in 10% aqueous methanolic sodium hydroxide for cleavage. Neutralization of this hydrolyzed solution and treatment with *p*-bromo- or *p*-chlorophenacyl halides produces the corresponding *p*-halophenacyl esters in yields greater than 70%. The elemental analyses of these derivatives (and earlier negative Zeisel tests) reveal that no alcoholic fragment is lost during saponification, and, thus, that mycoticin is a lactone and not an ester.

Acetylation of mycoticin with acetic anhydride in pyridine yields an octaacetate, mp 155.5–156°, which can be reconverted to mycoticin by mild alkaline hydrolysis. The nmr spectrum of the acetate shows 12 olefinic protons (complex multiplet at τ 2.3–4.5), 9 *H*COCOR protons (diffuse multiplet at τ 4.5–5.7), 24 acetoxy protons (closely spaced peaks centered at τ 7.9), and 12 C–CH_3 protons (a broad peak at τ 9.05), confirming the presence of six double bonds, eight hydroxyl groups, and four methyl groups in the parent pigment. Hydrogenation of mycoticin acetate produces a perhydro derivative exhibiting nmr peaks at τ 4.7–5.7 (9 H), 8.0 (24 H), and 9.15 (12 H) with no

(1) Taken in part from the doctoral dissertation of D. J. McCaustland, Yale University, 1960.

(2) R. C. Burke, J. H. Swartz, S. S. Chapman, and W. Huang, *J. Invest. Dermatol.*, 23, 163 (1954).

(3) The mycoticins, sharing structural features in common with other macrolides such as filipin and fungichromin, represent the first members of this class of antibiotics in which the polyene section of the carbon chain is conjugated to the lactone carbonyl group.

(4) In this discussion, "mycoticin" refers to the mixture of Ia and Ib isolated from the mycelium of *S. ruber* (ATCC 3348).

(5) Satisfactory carbon and hydrogen analyses were obtained for mycoticin, the dodecahydro derivative, the octaacetate, and the *p*-halophenacyl ester derivatives assuming the parent pigment to be a 1:1 mixture of Ia and Ib.

(6) K. Hirayama, *J. Am. Chem. Soc.*, 77, 383 (1955).

(7) P. Nayler and M. C. Whiting, *J. Chem. Soc.*, 3037 (1955).

(8) E. F. L. T. Anet, B. Lythgoe, M. H. Silk, and S. Trippett, *ibid.*, 309 (1953).

(9) Although it was not possible to separate mycoticin into pure Ia and Ib, the polytrimethylsilyl ether of the dodecahydro derivative yielded two closely spaced vpc components in equal amounts.