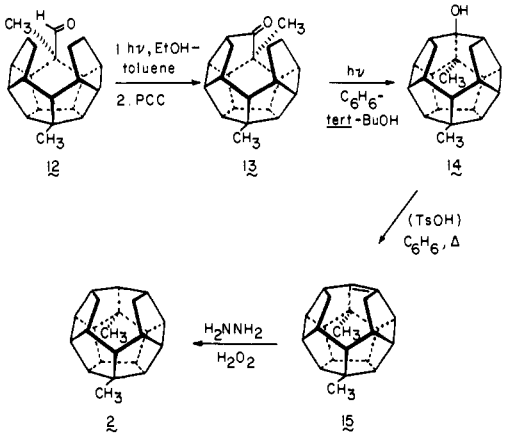
are seen to be somewhat long and the eight cyclopentane rings come in a variety of conformations. Of major interest are the distances between atoms where bonds are needed to complete the dodecahedrane framework. These are C(2)-C(6), 3.27; C(1)-C(20), 3.15; C(7)-C(20), 3.31 Å; all are well within achievable range.[15]

Because it was already obvious that the carbomethoxy group in **11a** could not be enticed into chemical reaction by photochemical means, the decision was made to proceed with aldehyde **12**. This substance was arrived at in excellent yield by sequential diisobutylaluminum hydride reduction and pyridinium chlorochromate oxidation.[16] The fact that the CHO group was bonded to a fully substituted carbon now had to be contended with. The literature dealing with the photochemical cyclization of aldehydes to cyclobutanols[17] leaves no doubt that these structural features are most conducive to decarbonylation. While **12** was certainly prone to carbon monoxide extrusion, a 29% yield of the epimeric "homo-Norrish" cyclopentanols could be realized in deoxygenated toluene–ethanol (9:1) solution at −78 °C (450-W Hanovia lamp, Pyrex). With subsequent pyridinium chlorochromate oxidation,



the diseco ketone **13** was obtained. Furthermore, not only could **13** be photocyclized reproducibly in high yield, but removal of the tertiary hydroxyl group in **14** and saturation of the double bond in **15** were encouragingly simple and efficient steps.

With arrival at the beautifully crystalline secododecahedrane **2** (mp 235–240 °C, sublime), a return to C_{2v} symmetry materializes, a phenomenon reflected in the appearance of only eight lines in its ^{13}C NMR spectrum.[18] The infrared spectrum is characterized by an unusually high absorption at 3150 cm^{-1}, assumed to be caused by the sterically compressed opposed methylene hydrogens. Molecular models of this decaquinane reveal that the opposed methylene groups must experience substantial steric repulsion adequate to force a skewed orientation.[20] Preliminary efforts to uncover a dehydrogenation catalyst effective on **2** or an isomerization catalyst which would cyclize **15** have yet to be successful. While investigations along the preceding lines continue, other workable solutions to this final maneuver and to the removal (or noninstallment) of the vestigial methyl groups are currently being examined.[19]

Supplementary Material Available: Final atomic (Table I) and anisotropic thermal parameters (Table II), bond lengths (Table III), bond angles (Table IV), and torsion angles (Table V) for **11b** (6 pages). Ordering information is given on any current masthead page.

[†]Presidential Fellow, 1979–1980.

(14) The crystals were triclinic, space group $P\bar{1}$, with $a = 8.517$ (3), $b = 8.738$ (2), $c = 13.191$ (5) Å; $\alpha = 70.86$ (3)°, $\beta = 80.94$ (3)°, $\gamma = 85.01$ (2)°; $d_{calcd} = 1.279$ g cm^{-3} for $Z = 2$ ($C_{24}H_{32}O_2$, M_r 352.52). The intensity data were measured with a Hilger–Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse-height discrimination). A crystal measuring approximately 0.15 × 0.35 × 0.6 mm was used for data collection. A total of 2472 reflections were measured for $\theta < 57°$, of which 2244 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure [Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368] and was refined by full-matrix least squares. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were refined isotropically. The final discrepancy indices are $R = 0.045$ and $wR = 0.059$ for the 2244 observed reflections. The final difference map has no peaks greater than ±0.2 e $Å^{-3}$.

(15) This is particularly so for ketone photochemistry in the solid state where it has been shown that the >=O···H_a—C< distance should be ≤2.5 Å, the >(HO)C···C< distance ≤3.5 Å, and the —H_2/O=C< angle approximately 90° with H_a ≤10° out of the carbonyl plane: Scheffer, J. R.; Dzakpasu, A. A. *J. Am. Chem. Soc.* **1978**, *100*, 2163.

(16) Mp 132–134 °C; ^1H NMR (δ, $CDCl_3$) 9.98 (s, 1 H), 3.8–0.7 (series of m, 21 H), 1.20 (s, 3 H), and 1.12 (s, 3 H); *m/e* calcd: 308.2140; found: 308.2150.

(17) (a) Orban, I.; Schaffner, K.; Jeger, O. *J. Am. Chem. Soc.* **1963**, *85*, 3033. (b) Schaffner, K. *Chimia* **1965**, *19*, 575; (c) Agosta, W. C.; Herron, D. K. *J. Am. Chem. Soc.* **1968**, *90*, 7025. (d) Coyle, J. D. *J. Chem. Soc. B* **1971**, 2254. (d) Lischewski, M.; Adam, G.; Serebryakov, E. P. *Tetrahedron Lett.* **1980**, 45.

(18) ^{13}C NMR (ppm, $CDCl_3$) 78.40 (s), 70.15 (d), 68.16 (d), 66.08 (d), 58.99 (d), 52.29 (d), 33.64 (q), and 32.58 (t).

(19) The National Institutes of Health (Grant No. AI-11490) provided the financial support which made this research possible.

(20) **Note Added in Proof**: Dr. Peter Engel (Bern) has recently confirmed the structural assignment to **2** by X-ray analysis.

^{13}C NMR Spectra of Carbonium Ions in the Solid State: The *sec*-Butyl Cation

Philip C. Myhre*[†] and Costantino S. Yannoni*

IBM Research Laboratory
San Jose, California 95193

Received May 27, 1980

The use of magic angle spinning in combination with NMR pulse techniques allows moderately high resolution ^{13}C NMR spectroscopy in the solid state.[1] With the inclusion of variable temperature capability,[2] solid-state ^{13}C NMR is a powerful tool for the study of very reactive intermediates. We report procedures that allow preparation of solid samples of thermally unstable carbonium ions and subsequent manipulation of samples for solid-state NMR studies at temperatures close to 77 K.[3] A study of the *sec*-butyl cation exemplifies these procedures.

2-Butanol-3-^{13}C (55 atom % enriched) was prepared from acetic acid-1-^{13}C by a standard sequence, and the alcohol was converted to 2-chlorobutane.[4,5] An intimate mixture of the alkyl chloride (1.5 mmol) and SbF_5 (~13 mmol) was deposited at ~10^{-5} torr on a cooled surface with the use of a vapor deposition apparatus (Figure 1). Our apparatus and deposition procedures are similar to those described by Saunders.[6] The O-ring joint on the reactor permits rapid detachment of the reactor base. Concentric jets

[†]Department of Chemistry, Harvey Mudd College, Claremont, CA 91711.

(1) Schaefer, J.; Stejskal, E. O.; Buchdahl, R. *Macromolecules* **1977**, *10*, 384.

(2) Fyfe, C. A.; Mossbrugger, H.; Yannoni, C. S. *J. Magn. Reson.* **1979**, *36*, 61.

(3) Well-resolved ^{13}C NMR spectra have been reported for stable carbonium ion salts. (Lyerla, J. R.; Yannoni, C. S.; Bruck, D.; Fyfe, C. A. *J. Am. Chem. Soc.* **1979**, *101*, 4770.)

(4) The sequence used was

$$CH_3{}^*CO_2H \xrightarrow[C_6H_5OH]{SOCl_2} CH_3{}^*CO_2C_6H_5 \xrightarrow[\text{diglyme}]{LiAlH_4} \xrightarrow[\text{distill}]{HOCH_2CH_2OH}$$

$$CH_3{}^*CH_2OH \xrightarrow{HBr} CH_3{}^*CH_2Br \xrightarrow[n\text{-}Bu_2O]{Mg} \xrightarrow{CH_3CHO} \xrightarrow[\text{distill}]{HOCH_2CH_2OH}$$

$$CH_3CH(OH){}^*CH_2CH_3 \xrightarrow[ZnCl_2]{HCl} CH_3CHCl{}^*CH_2CH_3 + CH_3{}^*CHClCH_2CH_3$$

(75%) (25%)

where * denotes the ^{13}C label.

(5) The small volume of the rotors (~60 μL) and the use of excess SbF_5 necessitated the use of ^{13}C-enriched samples to minimize data acquisition time.

(6) Saunders, M.; Cox, D.; Lloyd, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 6656.

0002-7863/81/1503-230$01.00/0

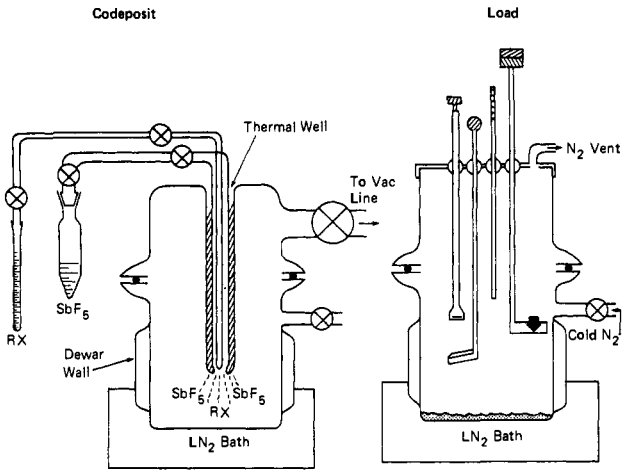


Figure 1. Sketch of apparatus used for codeposition and loading of solid mixtures of alkyl halide and antimony pentafluoride.

facilitate mixing of reactants. The Dewar jacket improves visual observation. After deposition, the reactor base was detached with a flow of cold nitrogen gas, and a cap equipped with a set of stainless steel tools was attached. A cold nitrogen purge was maintained during sample loading. The tools (Figure 1) consisted of a quick release holder for the rotor, a scoop, a tamping rod, and a combination rotor lid holder and screwdriver. By manipulating these tools, the solid could be transferred to the rotor and the threaded rotor lid secured at temperatures less than −160 °C.[7] The cold rotor is quickly dropped into a cup of liquid nitrogen. Transfer to the stator and spinning are initiated under liquid nitrogen before insertion into the precooled probe.[2]

NMR spectra of the 2-chlorobutane–antimony pentafluoride deposition are shown in Figure 2.[8] The spectra were obtained with ^1H–^{13}C cross polarization and decoupling of both ^{19}F and ^1H. Temperatures reported are those of the exiting propellant gas. The first spectrum, recorded at −85 °C, shows lines characteristic of the *sec*-butyl cation, represented in conventional form in eq 1, with C-1 and C-4 resonances at 22 ppm and C-2 and C-3

$$CH_3\text{–}CH^+\text{–}CH_2\text{–}CH_3 \rightleftharpoons CH_3\text{–}CH_2\text{–}CH^+\text{–}CH_3 \quad (1)$$

resonances at 170 ppm (Me_4Si). These values are close to the solution-state chemical shifts.[9] The resonance at 48 ppm is assigned to the methyl carbons of the *tert*-butyl cation. At lower temperatures, the same signals were observed with general line broadening and an increase in intensity of the *tert*-butyl cation signals.[10] Upon warming back to −85 °C, a spectrum identical with the first spectrum in the series was obtained. There was no significant spectral change upon warming to −60 °C.

The following conclusions may be drawn from the spectra: (1) Carbonium ions can be formed at low temperatures in the solid state by interaction of alkyl halides and SbF_5.[11] (2) At temperatures of ion formation (<−85 °C) the ^{13}C label was scrambled over the four carbon linear unit, but this scrambling is too slow to cause coalesence of the *sec*-butyl cation signals at −60 °C. (3) Rearrangement of *sec*-butyl to *tert*-butyl cation occurred to a limited extent under conditions of ion formation. (4) No convincing evidence is found at temperatures as low as −190 °C for a "static" *sec*-butyl cation.

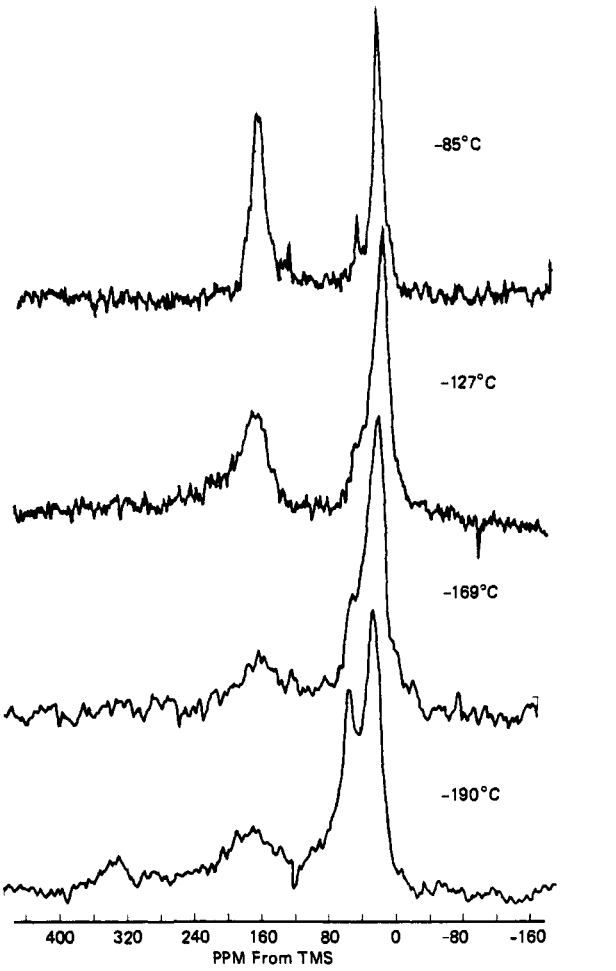
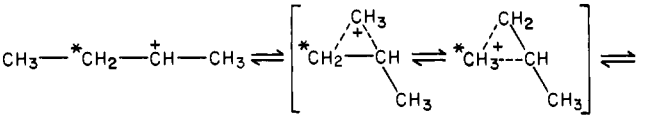


Figure 2. ^{13}C NMR spectra of the *sec*-butyl chloride–antimony pentafluoride mixture. Spectral parameters include ^{13}C–^1H cross polarization for 5 ms at 48-kHz Hartmann–Hahn matching,[1] 1-s delay between scans. Temperature in °C (ca. number of scans): −190 (14×10^4), −169 (56×10^3), −127 (15×10^4), −85 (52×10^3). Decoupling fields for ^1H and ^{19}F were 10 and 3 G, respectively.

These conclusions require comment. Independent preparations of the *tert*-butyl cation by codeposition of ^{13}C-enriched and unenriched *tert*-butyl chloride and SbF_5 support the first point. Chemical shifts observed for independently prepared samples of the *tert*-butyl cation agree with the signals at 48 and 330 ppm detected at −190 °C (Figure 2).[9] Scrambling of the four carbons of the *sec*-butyl cation is a low barrier process in solution which occurs via protonated cyclopropane intermediates (eq 2).[12]



$$^*CH_3\text{—}CH_2\text{—}\overset{+}{C}H\text{—}CH_3 \quad (2)$$

Saunders found that E_a = 7.5 kcal mol^{-1} and log A = 12.3 in solution.[13] Our spectra require that this process (eq 2) be facile, but the absence of coalescence at −60 °C indicates that the rate in a solid SbF_5 matrix is significantly slower than it is in solution.[14]

(7) It was also useful to partially fill the reactor with liquid nitrogen. This is done by increasing back pressure on the nitrogen gas passing through the liquid nitrogen heat exchanger.

(8) This sample was stored for several months under liquid nitrogen before spectral examination. Other samples, whose thermal history involved brief warming to ~−30 °C, gave spectra with the characteristic *sec*-butyl, but with much larger *tert*-butyl cation signals.

(9) Olah, G. A.; Donovan, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5026.

(10) The reversible increase in intensity of *tert*-butyl cation signals may be due to more efficient polarization by the *tert*-butyl methyl protons at low temperature.

(11) Although related studies of codeposits of *tert*-butyl chloride and SbF_5 indicate that it is possible to follow conversion of neutral reactants to the carbonium ion salt, the initial spectrum of this sample (−85 °C) showed complete conversion to the salt.

(12) Saunders, M.; Vogel, P.; Hagen, E. L.; Rosenfeld J. *Acc. Chem. Res.* **1973**, *6*, 53.

(13) Saunders, M.; Hagen, E. L.; Rosenfeld, J. *J. Am. Chem. Soc.* **1968**, *90*, 6882.

(14) Reported activation parameters (ref 12), indicate that the ^{13}C NMR spectrum of the *sec*-butyl cation should coalesce near −60 °C.

The barrier to the *sec*-butyl to *tert*-butyl cation rearrangement is high (E_a = 18 kcal mol^{-1}).[13] Nevertheless, the *tert*-butyl cation has been reported as a major byproduct in the reaction of *sec*-butyl halides with SbF_5 in solution at low temperature. Localized heating owing to ion formation has been suggested as the cause.[15] However, formation of the *sec*-butyl cation in the solid at temperatures below −85 °C results in only small amounts of the *tert*-butyl cation rearrangement product.[8]

The broad lines (150–500 Hz) of these carbonium ion spectra in solid SbF_5 preclude use of the line-width parameter as a measure of the exchange rate near the fast exchange limit.[16] An evaluation of the barrier for the hydride shift (eq 1) must rest on the detection of signals indicating slow exchange. The −190 °C spectrum shows no convincing evidence for a "static" *sec*-butyl cation. This result would not be surprising if solution-state barriers apply in the solid state. Thus, a recent estimate of $\Delta G^{\ddagger} < 2.4$ kcal mol^{-1} for the degenerate process shown in eq 1 is too low to permit detection of the static ion at −190 °C.[17] However, the rate of a chemical exchange process involving very small changes in atomic coordinates can be dramatically suppressed in the solid state,[18] and as noted above, the rate of carbon scrambling in the *sec*-butyl cation (eq 2) has been suppressed in solid SbF_5. If one can assume that this kind of suppression is operative for the degenerate hydride shift of the *sec*-butyl cation (eq 1), the barrier in solution is considerably less than 2.4 kcal mol^{-1}. Extension of these spectral measurements to lower temperatures and improvement in resolution may allow a more detailed structural characterization of the *sec*-butyl cation.[16,19]

Acknowledgment. The skilled assistance of R. D. Kendrick, A. J. Kalbin, and C. W. Rein in the design and construction of the apparatus is gratefully acknowledged. The help and encouragement of Dr. A. Diaz throughout the course of this work is appreciated. We are also pleased to acknowledge the National Science Foundation for support in the form of a Summer Faculty research stipend to P.C.M.

(15) Saunders, M.; Cox, D. W.; Ohlmstead, W. *J. Am. Chem. Soc.* **1973**, *95*, 3018.
(16) Some very recent results with much larger fluorine decoupling fields (~15 G) indicated that significant line narrowing can be achieved. Nevertheless, some residual line broadening may be anticipated owing to the nature of the sample. SbF_5 is believed to yield a variety of polyanions upon reaction with alkyl halides. Thus, solid-state samples of carbonium ion salts that we have prepared may lack the order characteristic of polycrystalline materials, and identical carbons in physically different sites would then yield a distribution of chemical shifts.[1]
(17) Saunders, M.; Kates, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 7082.
(18) Miller, R. D.; Yannoni, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 7396.
(19) For a recent discussion of structural representations of the *sec*-butyl cation, see: Schleyer, P. v. R.; Lenior, D.; Mison, P.; Liang, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 683.

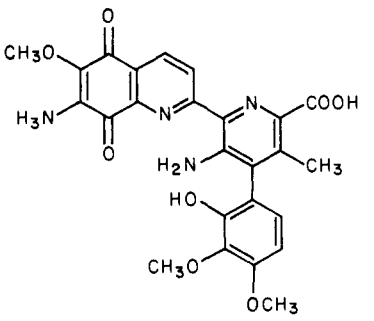
Interaction of Metal Ions with Streptonigrin. 1. Formation of Copper(II) and Zinc(II) Complexes of the Antitumor Antibiotic

Joseph Hajdu* and Ellen C. Armstrong

Department of Chemistry, Boston College
Chestnut Hill, Massachusetts 02167

Received May 16, 1980

The aminoquinone antibiotic streptonigrin (I), a metabolite of *Streptomyces flocculus*,[1] is one of the most effective agents for the treatment of human cancers.[2] Though showing activity against lymphoma, melanoma, cancers of breast, cervix, head, and neck, as well as against viruses, streptonigrin has a number of undesirable side effects, including most severe bone marrow depression.[3] This high toxicity presently precludes the clinical use of the antibiotic.[4]



I

There is evidence that streptonigrin exerts its antitumor action via (1) interference with cell respiration and (2) disruption of cell replication.[4] Both mechanisms are thought to involve participation of metal ions[5] and require an electron source as well as oxygen. Although the chemistry of streptonigrin–metal complexes has not been delineated, Cu^{2+} and Fe^{2+} are known to accelerate streptonigrin-induced DNA scission, while Co^{2+} has been shown to be inhibitory in the same process.[6] Mechanistic elucidation of the metal complexes of streptonigrin is important not only for understanding the mode of action of the antibiotic but also for developing a rational approach to improve its chemotherapeutic properties.

In this communication we report that reaction between the antitumor antibiotic and copper(II) or zinc(II) halides leads to the corresponding divalent metal chelates, which exhibit *remarkably different spectroscopic, electrochemical, and chemical redox properties*. Thus, addition of anhydrous zinc(II) or copper(II) chloride to an acetonitrile solution of streptonigrin produces a deep-brown solution of the corresponding metal complex (eq 1).

$$\mathrm{HSN} + \mathrm{M^{2+}} \rightleftharpoons {}^{-}\mathrm{SN{\cdot}M^{2+}} + \mathrm{H^{+}} \qquad (1)$$
$$\mathrm{M^{2+}} = \mathrm{Cu^{2+}},\ \mathrm{Zn^{2+}}$$

The spectra of the resulting metal derivatives differ from that of the antibiotic in a number of characteristic ways (Figure 1). For the zinc complex, the long-wavelength UV absorption is red shifted (375 → 400 nm) and its intensity enhanced in comparison with the spectrum of free streptonigrin. The 245-nm band of the parent antibiotic is split into a doublet, yielding a maximum at 235 nm and a shoulder at 255 nm, both decreased in intensity with respect to the absorption of the free ligand.

Complexation with copper(II) results in substantial broadening of the long-wavelength absorption (attributed to the quinoline quinone moiety) which is now centered at 415 nm. The pattern of the short-wavelength UV maxima remains quite similar to that of the parent antibiotic, except for a substantial decrease in the intensity of the 294-nm absorption band.

Formation of the complexes between streptonigrin and the metal ions is sensitive to the solvent and in aqueous media is strongly affected by the pH and the nature of the buffer.[7,8] Stepwise addition of $ZnCl_2$ to streptonigrin in 0.1 M Tris at pH 6.75 exhibits

(1) Rao, K. V.; Cullen, W. P. *Antibiot. Annu.* **1959**, 950.
(2) Davis, H. L.; VonHoff, D. D.; Henney, J. T.; Rozencweig, M. *Cancer Chemother. Pharmacol.* **1978**, *1*, 83.
(3) Wilson, W. L.; Labra, C.; Barrist, E. *Antibiot. Chemother. (Basel)* **1961**, *11*, 147.
(4) Lown, J. W. In "Bioorganic Chemistry"; Van Tamelen, E. E., Ed; Academic Press: New York, 1977; pp 95–121.
(5) Addition of chelating agents completely abolishes the biological activity of the drug. See: Bhuyan, B. K. In "Antibiotics"; Gottlieb, D.; Shaw, P. D., Eds.; Springer-Verlag: New York, 1967; p 175.
(6) Lown, J. W.; Sim, S. K. *Can. J. Chem.* **1976**, *54*, 2563–2572.
(7) For example, the dissociation constant of the streptonigrin–zinc complex in 0.1 M Tris, pH 7.0, was found to be 1.3 × 10^{-4} M, while in 0.0015 M citrate/0.015 M NaCl, pH 7.0, it is tenfold higher.
(8) Streptonigrin is most likely to be zwitterionic, at least in aqueous solution, yet considering the number of available protonation sites it is not clear where the H^+ is released when complexation takes place.

0002-7863/81/1503-232$01.00/0