Table I. 300-MHz Proton NMR Chemical Shifts for Ligand **2** in MeSO-d_6 (δ)

entry	sample	H_m	H_4	H_3	H_α, H_β
1	**2**·$Sr(ClO_4)_2$[a]	9.195	8.436[b]	8.197[c]	7.60-7.86
2	$(\mathbf{2})_2$·$Ba(ClO_4)_2$[a]	8.528	8.061[b]	7.659[c]	7.1-7.2
3	**2**·$KClO_4$ (2×10^{-2} M)	8.887	8.206[b]	7.952[c]	7.42-7.56
4	**2**-$KClO_4$ (2×10^{-2} M)[d] + [2.2.2]cryptand (2×10^{-3} M)[d]	8.815	8.138[b]	7.876[c]	7.36-7.47
5	**2**-$KClO_4$ (2×10^{-2} M) + 18-crown-6 (1×10^{-2} M)	8.815	8.136[b]	7.874[c]	7.36-7.46
6	**2**·$KClO_4$ (4×10^{-3} M)	8.962	8.262[b]	8.015[c]	7.47-7.62
7	**2**-$KClO_4$ (4×10^{-3} M) + [2.2.2]cryptand (4×10^{-2} M)	9.224	(8.05-8.08)[e]		7.35-7.55

[a] Reference 10. [b] Triplet, J = 7.7 Hz. [c] Doublet, J = 7.7 Hz. [d] Concentration approximate. [e] AB_2 multiplet.

[2.2.2]cryptand to a 4×10^{-3} M solution of **2**·$KClO_4$ led to a downfield shift of the Hm resonance, which finally, in the presence of excess cryptand, occurred at δ 9.224 (entry 7). In contrast, the addition of small increments of [2.2.2]cryptand to 2×10^{-2} M **2**·$KClO_4$ produced upfield shifts of all resonances of ligand **2** (entry 4).[15] Much larger quantities of added 18-crown-6 were required to produce these shifts (entry 5). The opposite ligand shifts observed when potassium is sequestered from different concentrations of **2**·$KClO_4$ indicate rapid equilibration among at least three species containing **2**. A simple explanation is that the chemical shifts listed in entry 7 of the table are due to the presence of metal-free **2**, whereas the upfield resonances at higher concentration (entries 4 and 5) may arise from significant amounts of a 2:1 complex analogous to the barium perchlorate complex.[10]

In order to estimate the stability constant (K_1) of **2**·$KClO_4$, we have used proton NMR to examine the uptake of potassium by 18-crown-6 when added to solutions of **2**·$KClO_4$ in Me_2SO-d_6. This process may be followed using the observed 18-crown-6 chemical shift, which is the population-weighted average of the shifts of the two species, 18-crown-6 and its potassium complex, in rapid equilibrium. To calibrate this marker, we first examined the concentration dependence of the NMR spectrum of 18-crown-6·$KClO_4$. Using δ 3.494 as the chemical shift for free 18-crown-6, it was calculated[16] that the chemical shift of the fully associated potassium complex is δ 3.543 and that the logarithm of the stability constant (log K_1) of 18-crown-6·$KClO_4$ is approximately 3.4. This is within experimental error of the potentiometrically determined value of 3.21 for log K_1 of 18-crown-6·$KClO_4$ in Me_2SO.[17] In the competition experiments, increments of solid 18-crown-6 were added to 2×10^{-2} M **2**·$KClO_4$ solutions in Me_2SO-d_6, causing slight upfield shifts of the resonances of **2**, as exemplified in entry 5 of the table. The concentration of "free" (solvated) potassium ion was calculated[18] from the observed 18-crown-6 chemical shift, which was also used with the integral ratio of **2**/18-crown-6 to determine the concentration of 18-crown-6·$KClO_4$. The concentrations of **2**·$KClO_4$ and free **2** were calculated by difference, resulting in a log K_1 for 2·$KClO_4$ of at least 4.1.[19]

We have estimated that the stability constant for **2**·$KClO_4$ is an order of magnitude greater than that of the corresponding 18-crown-6 complex in the same solvent. This effect is consistent with the larger dipole moment of imines and pyridines relative to ethers and contrasts with the reduced metal ion affinities observed in some pyridine-annelated crown ethers.[20] The difference may be largely conformational in nature,[21] since pyridine rings in the latter systems are relatively free to rotate their electric dipoles away from the molecular cavity. A similar effect could operate in sexipyridine,[22] making more rigid systems, such as azakekulenes,[23] particularly attractive candidates for strong and selective complexation of alkali metal ions.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Professor Cynthia J. Burrows is thanked for helpful discussions with the authors.

(16) Hartley, F. R.; Burgess, C.; Alcock, R. M. "Solution Equilibria"; Ellis Horwood: Chichester, U.K., 1980; pp 149-152.
(17) Kohltoff, I. M.; Chantooni, M. K., Jr. *Anal. Chem.* **1980**, *52*, 1039-1044.
(18) Reference 16, pp 109-111.
(19) This estimate is based on log K_1 (18-crown-6·$KClO_4$) = 3.21, assuming that there is insignificant formation of $(\mathbf{2})_2$·$KClO_4$. We consider 4.1 to be a lower limit for log K_1 (**2**·$KClO_4$), since including the 2:1 complex in the calculations leads to larger values for K_1.
(20) (a) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 475-479. (b) Jones, B. A.; Bradshaw, J. S.; Brown, P. R.; Christensen, J. J.; Izatt, R. M. *J. Org. Chem.* **1983**, *48*, 2635-2639.
(21) (a) Conformational destabilization of a complex of pyrido-18-crown-6 has been suggested.[20b] (b) As has been pointed out by a referee, stability constants for other pyridocrown ethers are not available in Me_2SO and solvent can have a large effect on log K. Ion preferences can even be inverted in some cases, e.g., ref 17.
(22) (a) Sexipyridine synthesis: Newkome, G. R.; Lee, H.-W. *J. Am. Chem. Soc.* **1983**, *105*, 5956-5957. (b) A metal-free synthesis of a sodium complex of a substituted sexipyridine has been claimed (Toner, J. L. *Tetrahedron Lett.* **1983**, *24*, 2707-2710), however, sodium analytical results were not reported.
(23) For a synthetic approach to a diazakekulene, see: Katritzky, A. R.; Marson, C. M. *J. Am. Chem. Soc.* **1983**, *105*, 3279-3283.

Reaction of a Carbon Analogue of Iodosylbenzene with Iron Porphyrins: Isolation and X-ray Structure of an Iron(II) Complex with O-C-C Moieties Inserted between Two Trans Iron-Nitrogen Bonds

Daniel Mansuy,*[1a] Jean-Paul Battioni,[1a] Irêna Akhrem,[1a] Daniel Dupré,[1a] Jean Fischer,[1b] Raymond Weiss,*[1b] and Irêne Morgenstern-Badarau[1c]

Laboratoire de Chimie de l'Ecole Normale Supérieure LA 32, 75231 Paris Cedex 05, France
Laboratoire de Cristallochimie, ERA 08 Université Louis Pasteur 67070 Strasbourg Cedex, France
Laboratoire de Spectrochimie des élêments de Transition, ERA 672, Université de Paris-Sud 91405 Orsay Cedex, France

Received May 22, 1984

High-valent Fe(IV)- or Fe(V)-oxo[2,3] complexes have been prepared upon reaction of iron porphyrins with potential oxygen atom donors. They are believed to be the active species involved in alkane hydroxylation and alkene epoxidation by iodosylbenzene catalyzed by cytochrome P-450[4] or iron porphyrins.[5] Their nitrogen analogues, Fe(IV)- or Fe(V)-imido (or iron(II) or iron(III) nitrene) complexes, seem to be formed upon oxidation of 1,1-dialkylhydrazines by cytochrome P-450,[6] and porphyrin-

(1) (a) Ecole Normale Supérieure. Present address for I. A.: Institute of Organo-Elements Compounds, Academy of Sciences, Moscow, U.S.S.R. (b) Université Louis Pasteur. (c) Université Paris-Sud.
(2) (a) Chin, D.-H.; La Mar, G. N.; Balch, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 5945-5947. (b) Chin, D.-H.; Balch, A. L.; La Mar, G. N. *J. Am. Chem. Soc.* **1980**, *102*, 1446-1448.
(3) Groves, J. T.; Haushater, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884-2885.
(4) (a) Ullrich, V. *Top. Curr. Chem.* **1979**, *83*, 67-104. (b) White, R. E.; Coon, M. J. *Annu. Rev. Biochem.* **1982**, *49*, 315-356.
(5) (a) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786-5791. (b) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243-6248 and references cited therein.
(6) Hines R. N.; Prough, R. A. *J. Pharmacol. Exp. Ther.* **1980**, *214*, 80-86.

0002-7863/84/1506-6112$01.50/0

iron–nitrene complexes, $Fe^{IV}{=}N{-}NR_2 \leftrightarrow Fe^{II}{\leftarrow}N{-}NR_2$, have been prepared by oxidation of such hydrazines and have been completely characterized.[7] Such iron nitrene complexes might be involved in the transfer of the *N*-tosyl moiety of the nitrogen analogue of PhIO, PhI=N—Tos, into aliphatic C–H bonds[8] or double bonds of alkenes,[9] catalyzed by iron(III) porphyrins.

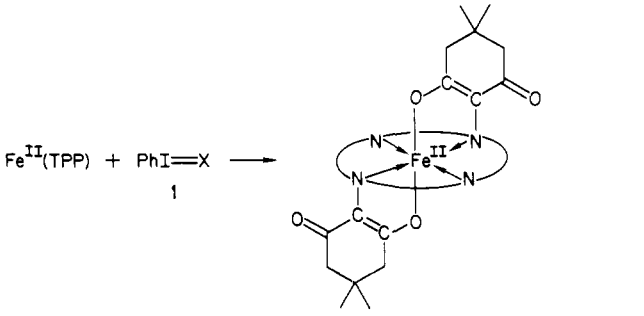
Their carbon analogues, the iron carbene complexes, seem to be formed upon oxidation of certain compounds by cytochrome P-450,[10] and several porphyrin–iron–carbene complexes have now been prepared and characterized.[11] It was thus tempting to study the reaction of the carbon analogues of PhIO, the iodonium ylides, PhI=CRR′, with iron porphyrins.

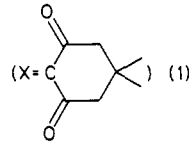
Fe=O (PhI=O) Fe=N—R (PhI=N—R)

Fe=CRR′ (PhI=CRR′)

This paper shows that compound **1** reacts quantitatively with iron(II) porphyrins leading to bis(*N*-alkyl)iron(II) complexes that involve two five-membered metallocycles coming from the insertion of a O–C–C moiety of **1** into two trans iron–nitrogen bonds.

Upon addition of $Fe^{II}(TPP)$[12] to compound **1**[13] (6×10^{-5} and 1.2×10^{-3} mol in deaerated toluene) and stirring of the solution at 50 °C for 0.5 h, a new complex, **2**, characterized by a Soret band at 462 nm[14] is formed. After purification by column chromatography (SiO_2, CH_2Cl_2:CH_3COCH_3, 8:2), complex **2** is obtained as green crystals in excellent yield (>95%) (eq 1).





Its elemental analysis (C, H, N) corresponds to Fe(TPP) having incorporated two X moieties, as well as its mass spectrum (DCI, I^-, CH_4) which exhibits a molecular peak at *m/e* 944 (100%) corresponding to $Fe(TPPX_2)$ and fragments at *m/e* 806 (30%) and 668 (25%) ($M^+ - X$ and $M^+ - 2X$). An X-ray analysis of a crystal[15] of complex **2**, obtained by slow crystallization from CH_2Cl_2–pentane, shows that it is a centrosymmetric hexacoordinate iron complex (Figure 1) with an unusual bis(metallocyclic) structure.

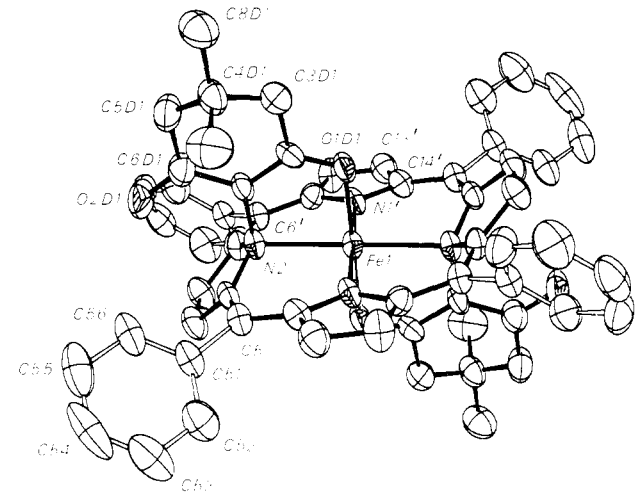


Figure 1. ORTEP plot of complex **2**. Hydrogen atoms are omitted for clarity. Ellipsoids are scaled to enclose 40% of the electronic density.

The two N-alkylated pyrrole nitrogens are much further away from the iron, Fe–N(alkyl) = 2.242 (5) Å, than are the other two, Fe–N(p) = 2.082 (5) Å. In all the mono-N-alkylated metal complexes[16] whose structures are known so far, the metal–N(alkyl) bond distances are always clearly longer, but in these complexes the metal is always displaced with respect to the four-nitrogen mean plane whereas in **2** the metal lies in this plane. The two Fe–N(p) bond lengths are longer than in the six-coordinate low-spin iron(II) porphyrins[17] but quite close to those in the high-spin ($S = 2$) $Fe(TPP)(THF)_2$.[18] Thus, bis N-alkylation as in **2** (N–C(X group) = 1.501 (6) Å, angle between N-alkylated pyrrole rings and Fe–N4 plane = 50.3°) leads to complexes in which the metal and the four nitrogens can form a planar coordination entity with a largely expanded core, which could be compatible with a high-spin state of the metal.

A high-spin Fe(II), $S = 2$, structure of complex **2** is in complete agreement with data from magnetic susceptibility measurements and EPR and ^1H NMR spectroscopies. From magnetic susceptibility measurements, it appears that the magnetic moment of crystalline complex **2** ($\mu = 5.4 \pm 0.05\ \mu_B$) is constant above 40 K and decreases to 4.5 μ_B as the temperature reaches 4 K, as expected for a quintet spin state.[19] No EPR signals are observed between 4.2 and 300 K, confirming the $S = 2$ ground state.

The overal range (35 to −42 ppm) and the shapes (broad peaks) of the ^1H NMR signals of complex **2** are also characteristic of a paramagnetic compound. A comparison of the ^1H NMR spectra of complex **2** and of its analogue prepared from a tetrakis(pentadeuteriophenyl)porphyrin partially deuterated on the pyrrole rings[7] allows one to assign the signals ($CDCl_3$, 20 °C) δ (from Me_4Si) 9.49 (8 H), 9.01 (4 H), and 6 (8 H) (phenyl H), 28.4 (4 H) and −42.4 (4 H) (two kinds of pyrrole H), and 6.05 (12 H), 7.61 (4 H), and 35.8 (4 H) (respectively, CH_3 and the two kinds of CH_2 groups of the X moieties).

Complex **2** is the first reported iron complex of a bis(*N*-alkyl)porphyrin. Whatever its mechanism of formation may be, it is the first porphyrin complex containing a FeOCCN five-membered metallocycle. An intermediate involving such a structure has been proposed[20] in the formation of "green pigments"

(7) (a) Mansuy, D.; Battioni, P.; Mahy, J. P. *J. Am. Chem. Soc.* **1982**, *104*, 4487–4489. (b) Mahy, J. P.; Battioni, P.; Mansuy, D.; Fischer, J.; Weiss, R.; Mispelter, J.; Morgenstern-Badarau, I.; Gans, P. *J. Am. Chem. Soc.* **1984**, *106*, 1699–1707.

(8) (a) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400–1401. (b) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728–6729.

(9) Mansuy, D.; Mahy, J. P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.*, in press.

(10) (a) Ullrich, V. "Biological Reactive Intermediates"; Jollow, D. J., Kocsis, J. J., Synder, R., Vaino, H., Eds.; Plenum Press: New York, 1977; pp 65–82. (b) Mansuy, D.; Battioni, J. P.; Chottard, J. C.; Ullrich, V. *J. Am. Chem. Soc.* **1979**, *101*, 3971–3973.

(11) (a) Mansuy, D. *Pure Appl. Chem.* **1980**, *52*, 681–690. (b) Battioni, J. P.; Chottard, J. C.; Mansuy, D. *Inorg. Chem.* **1982**, *21*, 2056–2062. (c) Battioni, J. P.; Dupre, D.; Guérin, P.; Mansuy, D. *J. Organomet. Chem.* **1984**, *265*, 53–64.

(12) Abbreviation: TPP = dianion of *meso*-tetraphenylporphyrin.

(13) Karele, B.; Neilands, O. *Zh. Org. Khim.* **1968**, *4*, 1818–1822.

(14) UV-vis (C_6H_6, 27 °C, λ (nm), ε (mM cm^{-1})): 462 (74.6), 557 (7.6), 610 (10.6), 742 (2.7).

(15) Crystal data: $C_{60}H_{48}N_4O_4Fe$, triclinic, $a = 12.755$ (3) Å, $b = 15.963$ (4) Å, $c = 12.104$ (3) Å, $\alpha = 91.77$ (2)°, $\beta = 105.46$ (2)°, $\gamma = 78.71$ (2)°, $Z = 2$, $\rho_{calcd} = 1.344$, $\rho_{obsd} = 1.32 \pm 0.02$ g cm^{-3}, space group $P\bar{1}$. For 3255 unique reflections having $(I) > 3\sigma(I)$, $R_F = 0.076$, $R_{wf} = 0.095$.

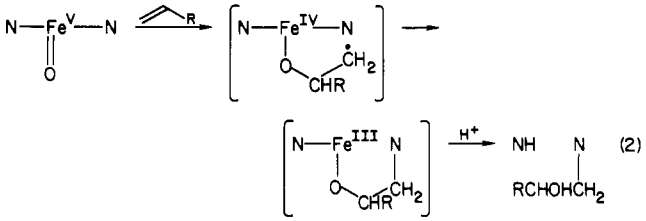
(16) (a) Anderson, O. P.; Lavallee, D. K. *J. Am. Chem. Soc.* **1977**, *99*, 1404–1409. (b) Anderson, O. P.; Lavallee, D. K. *Inorg. Chem.* **1977**, *16*, 1634–1640. (c) Lavallee, D. K.; Kopelove, A. B.; Anderson, O. P. *J. Am. Chem. Soc.* **1978**, *100*, 3025–3033. (d) Anderson, O. P.; Kopelove, A. B.; Lavallee, D. K. *Inorg. Chem.* **1980**, *19*, 2101–2107.

(17) Scheidt, W. R.; Gouterman, M. "Iron Porphyrins"; Lever, A. B. P., Gray, H. B., Ed.; Addison-Wesley: London, 1983; Vol. 1, pp 89–139.

(18) Scheidt, W. R.; Frisse, M. E. *J. Am. Chem. Soc.* **1975**, *97*, 17–21.

(19) Eisman, G. A.; Reiff, W. M. *Inorg. Chim. Acta* **1981**, *50*, 239–242 and references cited therein.

(*N*-(2-hydroxyalkyl)porphyrins) upon oxidation of monosubstituted alkenes (or alkynes) by cytochrome P-450[21] (eq 2).



(2)

Reaction of compound **1** analogues with iron porphyrins could be a good method for the preparation of model complexes containing this novel metallocyclic structure and to study their properties.

Acknowledgment. We thank C. Rolando and N. Morin (ENS, Paris) for the mass spectrometry measurements.

Registry No. 1, 35024-12-5; **2**, 91759-17-0; Fe^{II}(TPP), 16591-56-3.

Supplementary Material Available: Atomic positional and thermal equivalent parameters for all non-hydrogen atoms (Table I), thermal parameters for anisotropic atoms (Table II), listing of observed and calculated structure factors amplitudes (×10) (Table III) (21 pages). Ordering information is given on any current masthead page.

(20) Ortiz de Montellano, P. R.; Kunze, K. L.; Beilan, H. S.; Wheeler, C. *Biochemistry* **1982**, *21*, 1331-1339.
(21) Ortiz de Montellano, P. R.; Correia, M. A. *Annu. Rev. Pharmacol. Toxicol.* **1983**, *23*, 481-503.

"Quantamycin": A Computer-Simulated New-Generation Inhibitor of Bacterial Ribosomal Binding

Stephen Hanessian,* K. Sato, T. J. Liak, N. Danh, and D. Dixit

Department of Chemistry, Université de Montréal Montréal, Québec, Canada H3C 3V1

B. V. Cheney

The Upjohn Co., Kalamazoo, Michigan

Received April 27, 1984

In spite of the enormous advances in biotechnology[1,2] we still rely, by and large, on traditional methods for antibiotic discovery, and the need for conceptually novel approaches to drug development is omnipresent. A large group of clinically important antibiotics such as lincomycin, clindamycin, and erythromycin arrest bacterial infections in man by inhibition of protein biosynthesis at the ribosomal level.[3] Since lincomycin is known to bind in the region of the peptidyl transferase catalytic activity,[4] and in view of certain structural similarities with the peptidyl tRNA unit on the P site, it occurred to us that the incorporation

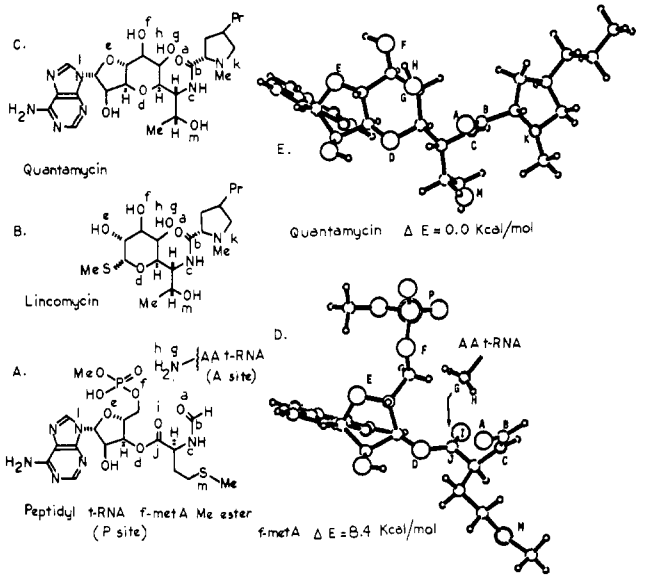


Figure 1. (A) (Left) Natural substrate (peptidyl tRNA) represented by *N*-formyl methionine terminal nucleotide. Letters a-m indicate possible foci for binding interactions at the ribosome. The LUMO in the conformation conducive to attack by the amino group (site g) of the aminoacyl tRNA (upper right) is an antibonding π orbital localized in the region of the ester unit (site j). The HOMO is associated with the amide oxygen atom (site a). (B) Corresponding foci for possible binding interactions of lincomycin at the P site of the ribosome. Site g may be a surrogate for the amino group of AA-tRNA. (C) Structure of quantamycin and convergent functional groups with the natural substrate. (D) (*N*-Formylmethionyl)adenylic acid methyl ester (model substrate for P site on ribosome) in the proposed binding conformation showing location of amino group of AA-tRNA. By means of the Duchamp molecular mechanics procedure,[6b] we have calculated the energy of this conformation to be 8.4 kcal/mol above the minimum energy conformation of the model compound. (E) Minimum energy conformation of quantamycin showing virtual convergence of sites a-h and l.

of additional features in its structure could result in a new-generation-type compound that might mimick the natural substrate.[5] By a combination of quantum and molecular mechanical calculations,[6] computer simulated superimpositions of energy-minimized structures, and considerations of frontier orbital theory,[7] we were able to generate a hybrid structure to which we have coined the name "quantamycin" (Figure 1). This model combines features present in lincomycin[8] and the terminal unit of peptidyl tRNA (represented as fMet-5'-adenylic acid methyl ester) and in its energy-minimized conformation shows a HOMO associated with the oxygen atom of the amide carbonyl group.[5] The purpose of this paper is to describe the total synthesis of quantamycin and to report on its biological activity.

Examination of the structure of our intended target reveals several potential difficulties associated with the construction of the strained, highly functionalized trans-fused perhydrofuropyran motif.[9-11] These challenges were overcome by a judicious choice of protecting groups and the development of novel manipulations

(1) See, for example Demain, A. L. *Science (Washington, D.C.)* **1983**, *219*, 709-714.
(2) Vourounakis, J. N.; Elander, R. P. *Science (Washington, D.C.)* **1983**, *219*, 703-709.
(3) Josten, J. J.; Allen, P. M. *Biochem. Biophys. Res. Commun.* **1964**, *14*, 241-244. Brock, T. D.; Brock, M. L. *Biochem. Biophys. Acta* **1959**, *33*, 274-277. Wisseman, C. L., Jr.; Smadel, J. E.; Hahn, F. E.; Hopps, H. E. *J. Bacteriol.* **1954**, *67*, 662-671.
(4) Monro, R. E.; Fernandez-Munoz, R.; Celma, M. L.; Vasquez, D. In "Drug Action and Drug Resistance in Bacteria, 1. Macrolide Antibiotics and Lincomycin"; Mitsuhashi, S., Ed.; University Park Press: Baltimore, 1971; pp 305-336.
(5) Cheney, B. V. *J. Med. Chem.* **1974**, *17*, 590-599.
(6) (a) Christoffersen, R. E. *Adv. Quantum Chem.* **1972**, *6*, 333-393. (b) Duchamp, D. J. In "Computer Assisted Drug Design"; Olson, E. C., Christoffersen, R. E., Eds.; American Chemical Society: Washington, DC, 1979; ACS Symp. Ser. No. 112, p 79.
(7) Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* **1969**, *41*, 1989-1997. Fukui, K. In "Molecular Orbitals in Chemistry, Physics and Biology"; Löwdin, P. O., Bullman, B., Eds.; Academic Press: New York, 1964; p 513.
(8) Magerlein, B. *Adv. Appl. Microbiol.* **1971**, *14*, 185-229.
(9) Sakata, K.; Sakurai, A.; Tamura, S. *Agric Biol. Chem.* **1974**, *38*, 1883-1890. Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1975**, *97*, 943-945.
(10) Hanessian, S.; Liak, T. J.; Dixit, D. *Pure Appl. Chem.* **1981**, *53*, 129-148; *Carbohydr. Res.* **1981**, *88*, C14-C19.
(11) Kim, K. S.; Szarek, W. *Can. J. Chem.* **1981**, *59*, 878-888. See also: Anzai, K.; Saita, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 169-174.

0002-7863/84/1506-6114$01.50/0