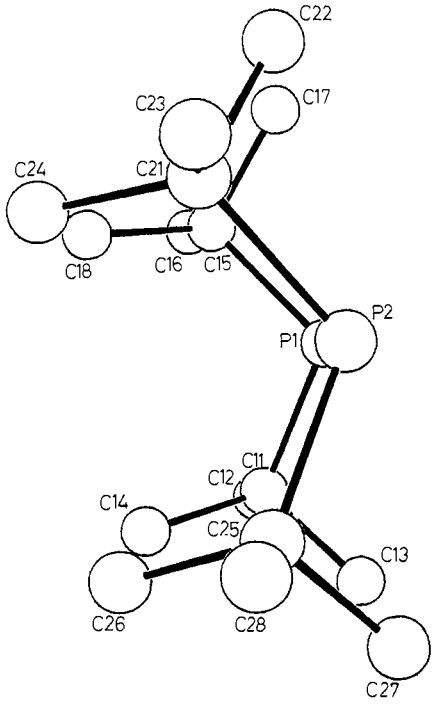


Figure 3. View down the P(2)-Hg-P(1) axis of 3. The Hg atom is obscured by P(2).

Thus, those on P(2) point down, away from the Cd_3 plane, those on P(3) are above it, and those on P(1) lie both above and below the plane. The Cd-methyl groups all lie essentially in the Cd_3 plane giving each Cd atom a novel planar three-coordinate geometry.[13] The Cd-P bond distances are all similar and range from 2.568 (4) to 2.598 (3) Å (2.585 (4) Å av) and compare well with the sum of the Bragg-Slater radii[14] for Cd(II) (1.55 Å) and P(1.00 Å). The Cd-C(methyl) distances range from 2.13 (2) to 2.18 (2) Å (2.16 (2) Å av). They may be compared to the Cd-C distance of 2.14 Å (av) in $[(Me_3SiCH_2)_2Cd](bipy)$.[15]

An ORTEP view of $Hg(t\text{-}Bu_2P)_2$ (3) is shown in Figure 2. As expected the central Hg atom has a two-coordinate linear geometry (P(1)-Hg-P(2) = 177.5 (1)°). The Hg-P bond lengths are similar at 2.442 (3) (Hg-P(1)) and 2.451 (3) (Hg-P(2)). The structure of 3 contains an interesting feature which concerns the orientation of the P-*t*-Bu groups and phosphorus lone pairs. Each phosphorus has a pyramidal geometry, however, the P-*t*-Bu groups on the two phosphides are eclipsed with respect to each other. A view along the P(1)-Hg-P(1) direction, which illustrates this feature is shown in Figure 3. Thus both phosphorus lone pairs occupy the same side of the molecule. This suggests that steric factors do not play an important role in determining the molecular geometry of 3 in the solid state. This may be due to the large size of the Hg atom.

Although the apparent M:P stoichiometries of 1 and 2 do not correspond to those of the binary compounds such as Zn_3P_2 and Cd_3P_2, we are currently exploring the use of these and related complexes as potential precursors to solid-state materials.

Acknowledgment. We thank the Robert A. Welch Foundation and the National Science Foundation for support. R.A.J. also thanks the Alfred P. Sloan Foundation for a fellowship (1985-1989).

Supplementary Material Available: Details of the synthesis and spectroscopic characterization of **1**, **2**, and **3**, the X-ray crystallography of **2** and **3**, the $^{31}P\{^1H\}$ NMR spectrum of **2**, table of least-squares planes for **2**, and tables of bond lengths, angles, positional parameters, and thermal parameters (17 pages); tables of observed and calculated structure factors (38 pages). Ordering information is given on any current masthead page.

(13) Sum of angles around Cd = 359.8 (4)° (av). For a rare example of three coordinate Zn, see: Al-Juaid, S. S.; Buttrus, N. H.; Eaborn, C.; Hitchcock, P. B.; Roberts, A. T. L.; Smith, J. D.; Sullivan, A. C. *J. Chem. Soc., Chem. Commun.* **1986**, 908. Deviations (Å) from the least-squares plane through Cd(1)-Cd(2)-Cd(3) and P(1) are as follows: P(1) 0.056 (4), Cd(1) -0.037 (1), Cd(2) -0.037 (1), Cd(3) 0.018 (1), P(2) 0.618 (4), P(3) -0.731 (4).

(14) Slater, J. C. *J. Chem. Phys.* **1964**, *41*, 3199.

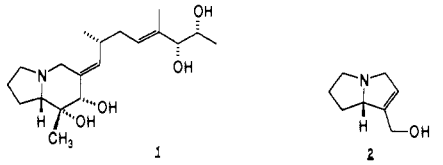
(15) Bushnell, G. W.; Stobart, S. R. *Can. J. Chem.* **1980**, *58*, 574. See also Khan et al. (Khan, O. F. Z.; Frigo, D. M.; O'Brien, P.; Hower, A.; Hursthome, M. B. *J. Organomet. Chem.* **1987**, *334*, C27) for the X-ray structure of bis[2-((dimethylamino)methyl)phenyl]cadmium(II) where Cd-C = 2.154 (8) Å.

Stereoelectronic Requirements of a Pd(0)-Catalyzed Cyclization. A Synthesis of *allo*-Pumiliotoxin 339B

Barry M. Trost* and Thomas S. Scanlan

Department of Chemistry, Stanford University
Stanford, California 94305
Received February 9, 1989

The widespread occurrence and diverse biological activity of indolizidine[1] and pyrrolizidine[2] alkaloids and the presence of many in only minute quantities from the natural sources have made them attractive research objectives. In asking how transition-metal-catalyzed allylic alkylations might solve the structural problems presented by these alkaloids, we targetted *allo*-pumiliotoxin 339B (**1**),[3] one of the most complex indolizidines, and supinidine (**2**),[4]



since both would derive from common chemistry in terms of construction of the basic nucleus. While many syntheses of supinidine exist,[5] the architecturally challenging pumiliotoxins—a diverse class of amphibian toxins[1,6]—have been successfully tackled synthetically only through the excellent efforts of the Overman group.[7]

These targets also provide an ideal format to probe the more general question regarding geometrical requirements of palladium-catalyzed cyclizations involving allylic alkylations. Examination of eq 1 reveals that cyclization mode "a" invokes an exocyclic transition state in terms of the orientation of the palladium complex with respect to the forming ring, whereas mode "b" invokes an endocyclic cyclization, a process that should become disfavored as the tether is shortened.[8,9] The facility of the en-

(1) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1, pp 1-274. Howard, A. S.; Michael, J. P. *The Alkaloids* **1986**, *28*, 183.

(2) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465. Letendre, L.; Smithson, W. A.; Gilchrist, G. S.; Bergert, E. O.; Hoagland, C. H.; Cimes, M. M.; Porvis, G.; Korach, J. S. *Cancer* **1981**, *47*, 437. Robins, D. J. *Fortschritte Chem. Org. Naterst.* **1981**, *41*, 8. Robins, D. J. *Adv. Heterocyclic Chem.* **1979**, *24*, 247. Warren, F. L. In *The Alkaloids, Chemistry and Physiology*; Manske, R. H., Ed.; Academic: New York, 1970; Vol. XII, p 319.

(3) Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron* **1984**, *40*, 1183.

(4) Men'shikov, G. P.; Gurevich, E. L. *J. Gen. Chem. USSR (Eng. Transl.)* **1949**, *19*, 1382.

(5) For a recent leading reference, see: Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755.

(6) For a recent structural study, see: Garraffo, H. M.; Edwards, M. W.; Spande, T. F.; Daly, J. W.; Overman, L. E.; Severini, C.; Erspamer, V. *Tetrahedron* **1988**, *44*, 6795.

(7) (a) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192. (b) Overman, L. E.; Goldstein, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 5360. (c) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669. (d) Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167. (e) Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901. (f) Overman, L. E.; Sharp, M. J.; Zablocki, J. A. *Abstracts of Papers*, National Meeting of the American Chemical Society, Toronto, Canada; American Chemical Society: Washington, DC, June 5-11, 1988; ORGN 77.

(8) Cf.: Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *Chem. Commun.* **1976**, 736.

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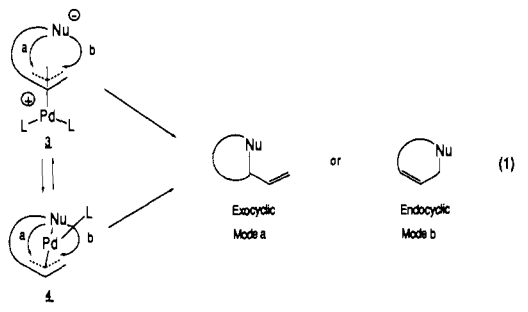
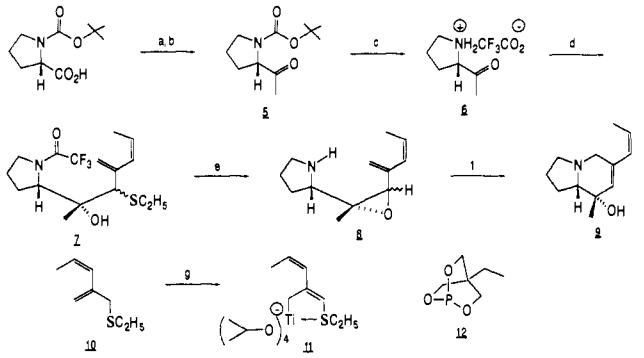


docyclic mode of reaction is highlighted by the preferential formation of eight- and nine-membered rings in lieu of the normally greatly perferred six and seven in many palladium-catalyzed cycloalkylations.[10] Furthermore, the mechanistic diversity in terms of reaction via **3** or **4** complicates the picture. Palladium complex **4** would form a cyclic product through a formal reductive elimination mechanism, and this mechanistic variation may lead to a new set of cyclization rules. To probe the geometrical requirements of these metal-catalyzed reactions in cases where the endocyclic mode of reaction would lead to six- or five-membered rings, a nucleophile which could react via either **3** or **4** was desirable. The suggestion from our previous work[11] that nitrogen might be such a nucleophile makes the alkaloid targets **1** and **2** particularly good tests.

The synthesis of the indolizidine precursor followed the route in Scheme I.[12] The mixture of epimers at the carbon bearing the ethylthio group in adduct **7** was irrelevant since this carbon was ultimately converted into a nonstereogenic center. A variety of Pd(0) catalysis conditions effected the cyclization of vinyl epoxide **8** but in inconsistent and irreproducible (24–50%) yields. Optimization of the reaction was achieved by employing a catalyst system consisting of $(dba)_3Pd_2{\cdot}CHCl_3$ and ligand **12** and adding water as a proton source. These conditions effected a cleaner transformation and provided indolizidine **9**[14] in satisfactory and reproducible yields.[15] Since the diastereomeric hydroxy sulfides **7**[14] were separable, each diastereomer as well as a 2.3:1 mixture of diastereomers was taken through this sequence. Each gave the identical indolizidine confirming the excellent diastereofacial selectivity of the addition to the amino ketone derived from **6**.

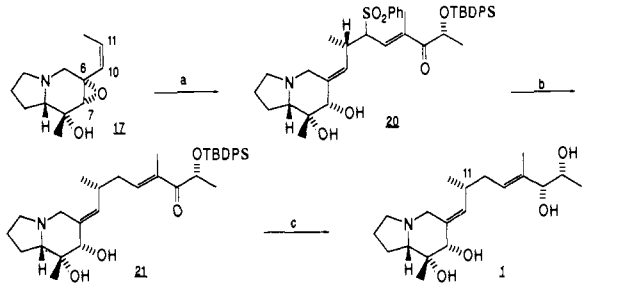
With the success of the 6-endo cyclization established, we turned our attention to the 5-endo case, which would lead to the pyrrolizidines. By using similar chemistry,[16] a series of cyclization substrates **13–16** were prepared. All attempts to cyclize any one of these to the pyrrolizidine failed.

Scheme I. Synthesis of Indolizidine Nucleus[a]

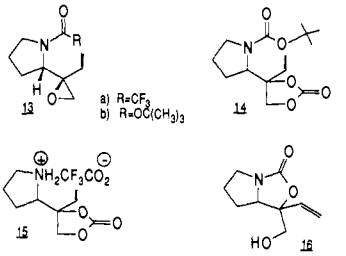


[a] (a) $(COCl)_2$, DMF, C_5H_5N; $CH_3NHOCH_3{\cdot}HCl$, C_5H_5N; 81%; (b) CH_3MgBr, THF, 0 °C, 91%; (c) CF_3CO_2H, CH_2Cl_2; (d) **11**, THF, −78 °C; $(CF_3CO)_2O$; 49–72% from **5**; (e) $(CH_3)_3OBF_4$, CH_2Cl_2O; NaOH, H_2O, CH_3OH, equiv of 60–81%; (f) 1.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 12 mol % **12**, 10 equiv of H_2O, THF, 65 °C, 66–73%; (g) *t*-C_4H_9Li, THF, −78 °C; $Ti(OC_3H_7\text{-}i)_4$, −78 °C.

Scheme II. A Synthesis of (+)-*allo*-Pumiliotoxin 339B[a]



[a] (a) **19**, 5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 20 mol % dppf, 10 equiv of H_2O, THF, room temperature; (b) 6% Na(Hg), Na_2HPO_4, CH_3OH; 24% overall; (c) LAH, THF, −20 °C; 68%.



In spite of the fact that the carbon termini of the π-allyl fragment are distorted from sp^2 hybridization and that the palladium does not depart but simply reorganizes from η^3 to η^2 coordination, the metal-catalyzed cyclizations bear a striking similarity to conventional cycloalkylations in their inability to effect a 5-endo cyclization. In considering reactions via structure **3** (eq 1), the palladium and its attendant ligands would appear to function like a simple leaving group in which the trajectory between the incoming nucleophile and the "departing palladium(0)" should approach 180°. Furthermore, reaction via structure **4** (eq 1) does not appear to be occurring with the substrates examined herein.[17]

The indolizidine **9**, readily available in enantiomerically pure form by this route, serves as an ideal precursor to *allo*-pumiliotoxin

(9) With carbon nucleophiles, cyclopropanes are normally preferred, but this fact may derive from a kinetic preference and does not test the feasibility of five-membered ring formation via a 5-endo trig cyclization. For an example of a palladium-mediated 5-endo trig cyclization, see: Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 3453. Genet, J. P.; Balabane, M.; Backvall, J. E.; Nystrom, J. E. *Tetrahedron Lett.* **1983**, *24*, 2745. However, also see: Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, 2871. Fugami, K.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 857.

(10) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743; **1978**, *100*, 3435; **1976**, *98*, 630. Martina, D.; Brzezowski, C. Unpublished work in these laboratories. For amine nucleophiles in Pd-catalyzed cyclizations, see: Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 8516. Trost, B. M.; Cossy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6881. Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332.

(11) Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779; *J. Org. Chem.* **1979**, *44*, 3451. Also, see: Larock, R. C.; Harrison, L. W.; Hsu, M. H. *J. Org. Chem.* **1984**, *49*, 3664.

(12) For an alternative preparation of ketone **3** and Cram diastereoselective additions to **4** see Overman and Goldstein.[7b] For preparation of **8**, see: Trost, B. M.; Scanlan, T. S. *Tetrahedron Lett.* **1986**, *27*, 4141. For preparation of vinyl epoxides via metalated allyl sulfides, see: Furuta, K.; Ikeda, Y.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2781.

(13) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. Tsuiji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.

(14) All new compounds have been characterized spectroscopically and elemental composition established by high resolution mass spectroscopy or combustion analysis.

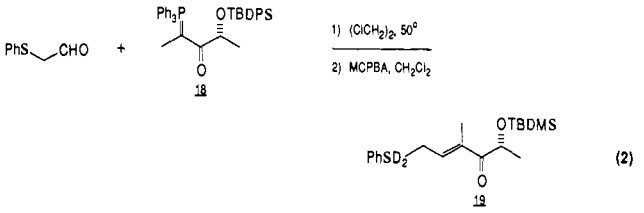
(15) Unpublished observations of Greves, N. and Brzezowski, C. in our laboratory have revealed dramatic effects of proton sources on palladium-catalyzed reactions of vinyl epoxides. For a recent related observation, see: Echavarren, A. M.; Tueting, D. R.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 4039.

(16) Synthesis of **11** involves addition of a metalated sulfide to the proline derived vinyl ketone in direct analogy to the synthesis of **5** and **6**. For conversion of **11** to **12**, see: Trost, B. M.; Angle, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 6123. Details of these syntheses will be published in due course.

(17) An endocyclic process via **4** requires the normally square-planar palladium complex to become tetrahedral.

339B in which a palladium-catalyzed alkylation can resolve the question of the stereochemistry of C(11) (see Scheme II). Hydroxyl-directed epoxidation of the trifluoroacetate salt of **9** with trifluoroperacetic acid provided the vinyl epoxide **17**.[14,18]

Transfer of stereochemistry from C(6) to C(11) requires (1) selective palladium initiated ionization from one conformer of the vinyl epoxide, (2) alkylation to be faster than equilibration of the π-allylpalladium intermediates, and (3) regioselective C–C bond formation at C(11) even though this generates a sterically congested exocyclic double bond. Construction of the alkylation partner **19**,[14] proceeds in a straightforward manner (eq 2) from



(2)

the known Wittig reagent **18**[7b] and phenylthioethanal.[19] Palladium(0)-catalyzed condensation of the vinyl epoxide **17** and allyl sulfone **19** *under neutral conditions, surprisingly also benefits from the addition of water*. Unlike the cyclization of **8**, the addition of water might have prevented generation of the requisite nucleophile since the basicity of the medium is limited to that of hydroxide in THF containing water. However, the success of the alkylation demonstrates that such concerns are unwarranted. Direct reductive desulfonylation of the crude alkylation product **20** provides a homogeneous ketone **21**.[14] Thus, faithful transfer of the stereochemical information from C(6) to C(11) using the palladium template has occurred. Threo-selective reduction as previously reported[7b] was accompanied by concommitant desilylation of the *tert*-butyldiphenylsilyl group to give *allo*-pumiliotoxin 339B, $[\alpha]_D^{26}$ +7.0, $[\alpha]_{577}^{26}$ +9.0°, $[\alpha]_{435}^{26}$ +17.0° (*c* 0.20, CH_3OH).[20] Comparisons of the ^1H and ^{13}C NMR spectra of our sample to those of authentic (+)-**1** confirm their identity.

The present work establishes the geometric boundary for endo-type palladium-catalyzed cycloalkylations to be between five and six and suggests an astonishing similarity of a palladium cationic leaving group to a conventional leaving group. The virtue of the palladium template to control conformational behavior and thereby transmit stereochemical information along conformationally mobile systems[21] demonstrates the uniqueness of "palladium leaving groups". With respect to pumiliotoxin, the use of palladium-catalyzed alkylations of vinyl epoxides provides a facile entry into the basic indolizidine ring system, allows a concise convergent strategy, and controls the creation of the proper stereochemistry at C(11) by chirality transfer. We believe this sequence is potentially a quite general approach to this intriguing alkaloid family.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences Institute, for their generous support of our programs. We thank Professor Larry Overman and Dr. Steven W. Goldstein for detailed experimental procedures for their synthesis of *allo*-pumiliotoxin B, for spectra of authentic samples, and for unpublished rotation data.

Supplementary Material Available: Characterization data (IR, ^1H NMR, and MS) for **8**, **9**, **17**, **19**, and **21** (2 pages). Ordering information is given on any current masthead page.

(18) A major byproduct in which the 10,11 rather than the 6,7 double bond has been epoxidized arises. The stereochemistry of **15** derives from the successful completion of the synthesis. For an amino-olefin epoxidation, see: Quick, J.; Khandelwal, Y.; Meltzer, P. C.; Weinberg, J. S. *J. Org. Chem.* **1983**, *48*, 5199.

(19) Toyushima, K.; Okuyama, T.; Takayuki, F. *J. Org. Chem.* **1978**, *43*, 2789.

(20) Overman and Goldstein record the following rotations: $[\alpha]_D^{25}$ +8.8°, $[\alpha]_{578}^{25}$ +6.8°, $[\alpha]_{435}^{25}$ +15.0°. We thank these workers for their unpublished data.

(21) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1979**, *101*, 6756.

Induced Dimerization of Tetrakis(*p*-sulfonatophenyl)porphine and Metalloderivatives by a Polyammonium Macrocycle [32]-$N_8H_8^{8+}$

Paul Firman and Ralph G. Wilkins*

Department of Chemistry, New Mexico State University Las Cruces, New Mexico 88003

Stanislaw P. Kasprzyk

Institute of Organic Chemistry Polish Academy of Science Warsaw, Poland

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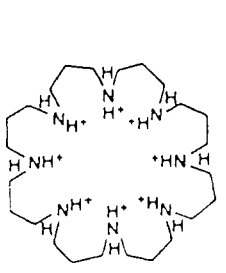
In this communication we report the induced dimerization of negatively charged porphyrins in *micromolar* concentrations by a 32-membered highly protonated macrocycle.

Polyammonium macrocycles and macropolycycles have been most studied as anion receptors.[1] The macrocycle 1,5,9,13,17,21,25,29-octaazacyclodotricontane [32]-N_8 is octaprotonated in weakly acid solution $N_8H_8^{8+}$, **1**, and binds strongly to multicharged anions.[2-4] Modification of electrochemical[4,5] and photochemical[6] properties as well as chemical reactivity[7,8] of the complexed anion has been reported.

It occurred to us that there might be strong electrostatic attraction between $N_8H_8^{8+}$ and the negatively charged porphyrin **2** (a) R = SO_3^-, H_2TPPS^{4-}. Examination of space-filling models (compare **1** and **2**) shows that the $-SO_3^-$ groups are quite close



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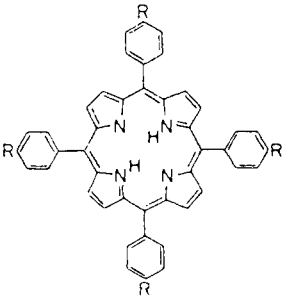

2a R = SO_3^-
2b R = CO_2^-

to alternating NH_2^+ groups on the macrocycle. Spectral titration of H_2TPPS^{4-} with $N_8H_8^{8+}$ (prepared according to ref 3) at pH 6.0[9] gave an isosbestic at 403 nm and indicated formation of a single, very stable, 2:1 adduct (eq 1). A similar behavior was

$$2H_2TPPS^{4-} + N_8H_8^{8+} \rightleftharpoons (H_2TPPS^{4-})_2{\cdot}NH_8^{8+} \qquad K_1 \quad (1)$$

observed when the visible region was utilized. The value of K_1

(1) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89.

(2) Dietrich, B.; Hosseini, M. W.; Lehn, J.-M.; Sessions, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 1282.

(3) Dietrich, B.; Hosseini, M. W.; Lehn, J.-M.; Sessions, R. B. *Helv. Chim. Acta* **1983**, *66*, 1262.

(4) Peter, F.; Gross, M.; Hosseini, M. W.; Lehn, J.-M.; Sessions, R. B. *J. Chem. Soc., Chem. Commun.* **1981**, 1067.

(5) Peter, F.; Gross, M.; Hosseini, M. W.; Lehn, J.-M. *J. Electroanal. Chem.* **1983**, *144*, 279.

(6) Manfrin, M. F.; Moggi, L.; Castelvetro, V.; Balzani, V.; Hosseini, M. W.; Lehn, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 6888.

(7) Macrocyclic polyamines, in particular the [24]-N_6O_2 macrocycle, 1,13-dioxa-4,7,10,16,19,23-hexaazacyclotetracosane, catalyze the hydrolysis of ATP, ADP, pyrophosphate, and phosphate derivatives: Hosseini, M. W.; Lehn, J.-M.; Mertes, M. P. *Helv. Chim. Acta* **1983**, *66*, 2454; **1985**, *68*, 818. Hosseini, M. W.; Lehn, J.-M.; Maggiora, L.; Mertes, K. B.; Mertes, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 537. Hosseini, M. W.; Lehn, J.-M. *J. Am. Chem. Soc.* **1987**, *109*, 7047. Yohannes, P. G.; Mertes, M. P.; Mertes, K. B. *J. Am. Chem. Soc.* **1985**, *107*, 8288. Yohannes, P. G.; Plute, K. E.; Mertes, M. P.; Bowman-Mertes, K. *Inorg. Chem.* **1987**, *26*, 1751.

(8) Kujundzic, N.; Wilkins, P. C.; Wilkins, R. G.; Kasprzyk, S. P. Paper 135, 196th National Meeting of the American Chemical Society: Los Angeles, CA; American Chemical Society: Washington, DC, September 1988.

(9) In this pH region the dominant species are as shown. The pK_a of $N_8H_8^{8+}$ (6.50[2,3]) is even likely to be raised by interaction with the anion (see Bencini, A.; Bianchi, A.; Garcia-España, E.; Giusti, M.; Mangani, S.; Micheloni, M.; Orioli, P.; Paoletti, P. *Inorg. Chem.* **1987**, *26*, 3902.

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