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Molecular Recognition of Pyrophosphate by 1,13-Dioxa-4,7,10,16,19,22-hexaazacyclotetracosane (OBISDIEN) and by Its Mononuclear and Dinuclear Copper(II) Complexes. A Thermodynamic and Molecular Mechanics Study

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The hexabasic macrocyclic ligand 1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane ([24]aneN$_6$O$_2$ or OBISDIEN) forms a variety of cationic species including mono- through hexaprotonated forms of the macrocycle in the absence of metal ions as well as both mononuclear and dinuclear copper(II) complexes. The Cu(II) complexes also form protonated, unprotonated, and hydroxylated species. These cationic hosts "recognize" certain bridging groups that have the suitable size and shape to bridge the two metal ions and coordinate them simultaneously. This paper describes the ability of OBISDIEN and its mononuclear and dinuclear Cu(II)—OBISDIEN complexes to "recognize" the pyrophosphate bridging group and to form complexes that exist in a number of protonated forms. In all, 48 individual species are identified. The nature of the bonding between the pyrophosphate, OBISDIEN, copper(II) ion, and one or more hydrogen ions is discussed. Molecular mechanics calculations show that the dicopper(II) OBISDIEN complex is able to adopt several low energy conformers with widely differing Cu to Cu separations that allow for coordination of bridging ligands of differing lengths.

Introduction

The macrocycle OBISDIEN, **1**, has six secondary amino groups consisting of two diethylenetriamine moieties separated by ethyl ether bridges, imparting considerable flexibility to the ligand which can assume conformations ranging from a shorter bowl-shaped configuration to an extended form and thus can adapt to a variety of complexation requirements and guest dimensions.

The OBISDIEN protonation constants and stability constants with Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} were reported previously.[1] The flexible geometry was also found to coordinate one metal ion, two metals ions, bridging hydroxyl, ethylenediamine, imidazole, and, in the case of dinuclear Co^{2+}, an oxygen molecule.[1] Coughlin et al.[2] reported the crystal structure of the dicopper(II) imidazolate-bridged OBISDIEN, and later Coughlin and Lippard[3] reported a μ-hydroxo—μ-perchlorato-bridged dicopper(II) OBISDIEN crystal structure. Structures of binuclear Cu(II) complexes of OBISDIEN with bridging azide have been reported by Lehn et al.,[4] in which paper is also reported a dinuclear copper(II) complex with the related ligand 24-aneN$_2$O$_6$ (1,4,7,13,16,19-hexaoxo-10,21-diazacyclotetracosane). The azide in the dicopper(II) OBISDIEN complex bridges in a lengthwise (-κN:$\kappa N''$) fashion, with a copper to copper separation of 5.973 Å, while the azide in the dicopper(II) 24-aneN$_2$O$_6$ complex bridges in an end-on (-κN:κN-) fashion with a concomitant shorter Cu to Cu separation of 3.162 Å. The dinuclear OBISDIEN dicobalt(II) complex forms a dioxygen complex while leaving an uncoordinated site (probably an

aqua site) on each metal center. This dioxygen complex has been employed to study the intramolecular oxidation of λ-bound oxalate,[5–8] ketomalonate,[8,9] phosphite,[10] catechol,[11] tiron,[11] 3,4-diaminobenzoate,[12] and 1,2-diaminobenzene.[12]

Other guests studied with metal complexes of OBISDIEN as hosts include malonate,[13] phosphonous formate,[13] glycinate,[13] and sulfate.[14] In each of the above systems, a determination was made of the nature and number of protonated guest—host adducts in the absence of metal ions. Similar studies have been made by Hosseini et al.[15–17] of the affinities of protonated forms of OBISDIEN for AMP, ADP, and ATP.

Most of the dinuclear complexes of OBISDIEN that have been investigated involved Co^{2+}. Because cobalt does not fully complex OBISDIEN below neutral p[H] values, it was decided to utilize Cu^{2+} instead and to study the interaction of OBISDIEN with a new guest, pyrophosphate. This system is of considerable interest since it is a reasonable candidate for binding by OBISDIEN and its copper(II) complexes and because pyrophosphate is a constituent in many organic phosphates and the nucleotides. This report utilizes the potentiometric method for the determination of the species in solution formed between

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(1) Motekaitis, R. J.; Martell, A. E.; Lecomte, J. P.; Lehn, J. M. *Inorg. Chem.* **1983**, *22*, 609.

(2) Coughlin, P. K.; Dewan, J. C.; Lippard, S. J.; Watanabe, E.; Lehn, J. M. *J. Am. Chem. Soc.* **1979**, *101*, 265.

(3) Coughlin, P. K.; Lippard, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3228.

(4) Commarmond, P.; Plumere, P.; Lehn, J. M.; Agnus, Y.; Louis, R.; Weiss, R.; Kahn, O.; Morgenstern-Badarau, I. *J. Am. Chem. Soc.* **1982**, *104*, 6330.
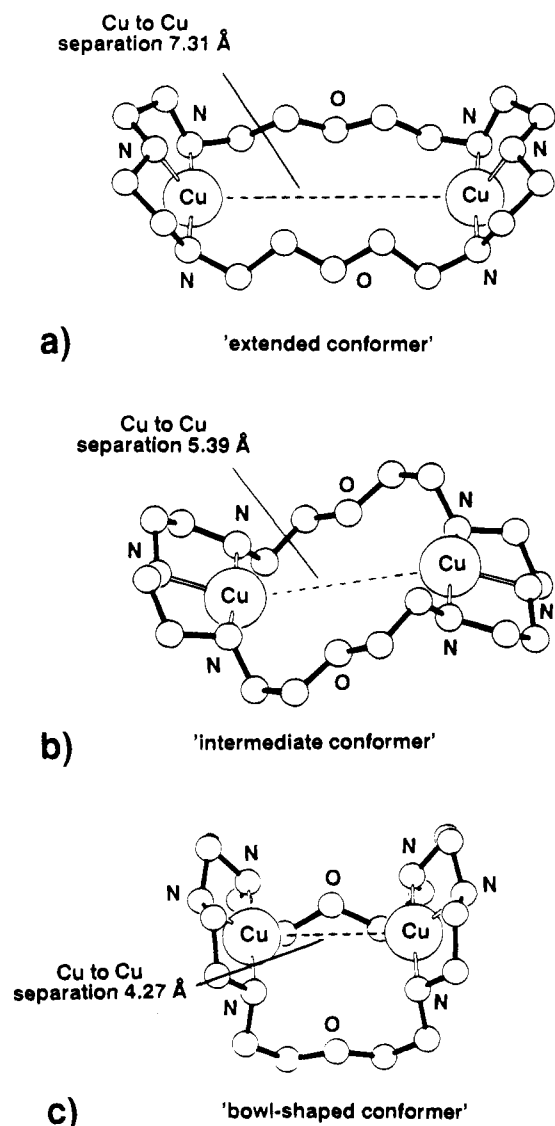
(5) Martell, A. E.; Motekaitis, R. J. *J. Chem. Soc. Chem. Commun.* **1988**, 915.

(6) Martell, A. E.; Motekaitis, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 8059.

(7) Martell, A. E. *J. Inclusion Phenom.* **1989**, *7*, 99.

(8) Martell, A. E.; Motekaitis, R. J. In *Dioxygen Activation and Homogeneous Catalytic Oxidation*; Simandi, L. I., Ed.; Elsevier: Amsterdam, 1991; pp 331–336.

(9) Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1991**, *30*, 694.

(10) Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1994**, *33*, 1032.

(11) Szpoganicz, B.; Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1990**, *29*, 1467.

(12) Rosso, N. D.; Szpoganicz, B.; Motekaitis, R. J.; Martell, A. E. *Inorg. Chim. Acta*, in press.

(13) Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1992**, *31*, 5534.

(14) Motekaitis, R. J.; Utley, W. B.; Martell, A. E. *Inorg. Chim. Acta* **1993**, *212*, 15.

(15) Hosseini, M. W.; Lehn, J. M. *Helv. Chim. Acta* **1987**, *70*, 1312.

(16) Hosseini, M. W.; Lehn, J. M.; Mertes, M. P. *Helv. Chim. Acta* **1983**, *66*, 2454.

(17) Hosseini, M. W.; Lehn, J. M.; Mertes, M. P. *Helv. Chim. Acta* **1985**, *68*, 818.

Cu to Cu
separation 7.31 Å

a) 'extended conformer'

Cu to Cu
separation 5.39 Å

b) 'intermediate conformer'

Cu to Cu
separation 4.27 Å

c) 'bowl-shaped conformer'

Figure 1. Three low energy conformers for the dicopper(II) OBISDIEN complex generated by MM calculation in this work, showing the energy minimized Cu--Cu separations calculated. MM calculations were carried out using the SYBYL program.[19]

pyrophosphate, OBISDIEN, and Cu^{2+} ion as a function of pH and the stability constants that govern the interaction between the species formed.

Experimental Section

Materials. The following reagents were used: reagent grade $CuCl_2 \cdot 2H_2O$ obtained from Matheson Coleman & Bell, reagent grade $Na_2P_2O_7 \cdot 10H_2O$ obtained from Fisher Scientific Co., GR grade KCl obtained from EM Chemical Co., and CO_2-free Dilut-it ampoules of KOH from J. T. Baker Inc. OBISDIEN, in the form of colorless hexahydrobromide solid, was kindly supplied by Dr. Ichiro Murase of Dojindo Co., Kumamoto, Japan. Its purity was checked by NMR and by potentiometric titration. The Cu^{2+} solution was standardized by titration with primary standard EDTA in a NH_4OH/NH_4Cl buffer using Murexide (1% in NaCl) as an indicator. The KOH solution was standardized by titration against primary standard potassium acid phthalate using phenolphthalein as an indicator. A Gran's plot determination of the carbonate content of the KOH solution found 1.8% relative to KOH. This is under the acceptable limit of 2%.[18]

Potentiometric Apparatus. Each aqueous system under consideration was measured in a 100 mL jacketed cell thermostated at 25.0

Table 1. Overall Stability Constants for the Cu(II)—OBISDIEN System ($\mu = 0.100$ M KCl, 25.0 °C Bd = L = OBISDIEN, M = Cu^{2+}, H = H^+, OH = OH^-)

stoichiometry						stepwise
Bd	Cu	H	$\log \beta^a$	lit.^{b}	stepwise quotient K	$\log K^a$
1	1	0	16.21	16.46	[ML]/[M][L]	16.21
1	1	1	24.01	24.47	[MHL]/[ML][H]	7.81
1	1	2	31.77	31.93	[MH$_2$L]/[MHL][H]	7.76
1	1	3	35.21	35.38	[MH$_3$L]/[MH$_2$L][H]	3.44
1	2	0	26.99	27.30	[M$_2$L]/[ML][M]	10.79
1	2	−1	20.61	20.79	[M$_2$L]/[M$_2$LOH][H]	6.38
1	2	−2	10.12	10.39	[M$_2$LOH]/[M$_2$L(OH)$_2$][H]	10.49

^{a} This work. $\sigma_{fit} = 0.0046$ (1:1); $\sigma_{fit} = 0.0050$ (2:1 Cu^{2+}:Bd). ^{b} 25.0 °C, $\mu = 0.100$ M KNO$_3$, stepwise, refs 20 and 1, OBISDIEN·6HCl.

± 0.05 °C by a mechanically refrigerated circulating water bath. KCl was employed as a supporting electrolyte to keep the ionic strength constant at 0.100 M. An inert atmosphere in the cell was maintained by bubbling prepurified, humidified argon through the solution. A Corning No. 476022 glass electrode with a matched calomel reference extension electrode was used with a Corning Model 150 pH meter.

Calibration. The apparatus was calibrated in terms of $-\log[H^+]$ (p[H]) by titration of a very dilute solution of HCl from p[H] 2.3 to about 3.5 in 0.100 M KCl at 25.0 °C and by adjusting the meter so as to minimize the calculated p[H] vs observed values. As a practical matter, a one point calibration was performed in day to day work.

Procedure. Depending on the stoichiometry, 0.1—0.2 mmol quantities of reagents were used in each system and the starting volume was always 50.00 mL. p[H] measurements were made as KOH was added to the system in small increments. pK_w for water at $\mu = 0.10$ M is 13.78.[18] Each titration was performed in such a manner as to collect 10—11 equally spaced points per equivalent of base added, with at least 10 increments added beyond that required. Thus the ligand-alone titration provided 71 points, the 1:1 Cu^{2+}:OBISDIEN system provided 79 points, the 2:1 Cu^{2+}:OBISDIEN titration provided 86 points, the diphosphate titration provided 64 points, and the Cu—pyrophosphate system provided 78 points. Also, the 1:1:1 Cu^{2+}:OBISDIEN:pyrophosphate solution provided 76 points, the 2:1:1 Cu^{2+}:OBISDIEN: pyrophosphate system provided 83 points, and the 1:1 OBISDIEN: pyrophosphate solution provided 85 points. Although in most cases preliminary titrations were performed, these were only compared for similarity to, but never averaged with, the final determinations. Beyond the preliminary titration only a single final titration was used in the calculations.

Calculations. The goodness of fit parameter is a measure of the ability to duplicate the experimental curve with the model chosen and is computed as follows:

$$\sum_{fit} = (U/N)^{1/2} N = \sum w$$

$$U = \sum w(p[H]_{obs} - p[H]_{calcd})^2$$

$$w = 1/(p[H]_{i+1} - p[H]_{i-1})^2$$

where $i = i$th titration point.

The program BEST was used along with the volume of KOH and pH data to compute all equilibrium constants.[18] Species distribution diagrams were computed from the equilibrium constants with the help of program SPE[18] and plotted on a LaserJet with SPEPLOT.[18]

Molecular Mechanics Calculations. These were carried out using the program SYBYL[19] running on a Silicon Graphics Indigo computer. The TAFF[19] force field present in SYBYL was used for all the MM calculations, with the addition of force constants to describe the Cu—N bonds and the coordination geometry of the Cu(II). A Cu—N ideal bond length of 2.03 Å was used, together with a Cu—N force constant of 200 kcal·mol^{-1}·Å^{-2}. The square planar geometry of the Cu(II) and four nitrogen donors was generated using a force constant of 0.005

(18) Martell, A. E.; Motekaitis, R. J. *Determination and Use of Stability Constants*, 2nd ed.; VCH Publishers: New York, 1992.

(19) (a) SYBYL program, available from TRIPOS Associates, 1699 South Hanley Road, St. Louis, MO. (b) Clarke, M.; Cramer, R. D.; Vanopdenbosch, N. *J. Comput. Chem.* **1989**, *10*, 982.

Table 2. Overall Stability Constants and Stepwise Recognition Constants for the Interaction of OBISDIEN with Pyrophosphate ($\mu = 0.100$ M KCl, 25.0 °C Bd = L = OBISDIEN, Pp = pyrophosphate^{4-}, H = H$^+$)

stoichiometry					stepwise	p[H] at		
Bd	Pp	H	log β^a	stepwise quotient K	log K^a	max concn	principal equilibrium K'	log K'
1	1	1	11.66	[BdPpH]/[BdH][Pp]	2.07	9.5	[BdPpH]/[BdH][Pp]	2.07
1	1	2	20.88	[BdPpH$_2$]/[BdH$_2$][Pp]	2.41	9.2	[BdPpH$_2$]/[BdH$_2$][Pp]	2.41
1	1	3	30.18	[BdPpH$_3$]/[BdH$_3$][Pp]	3.44	8.9	[BdPpH$_3$]/[BdH$_2$][PpH]	3.31
1	1	4	39.58	[BdPpH$_4$]/[BdH$_4$][Pp]	5.21	8.4	[BdPpH$_4$]/[BdH$_3$][PpH]	4.44
1	1	5	47.51	[BdPpH$_5$]/[BdH$_5$][Pp]	9.35	7.2	[BdPpH$_5$]/[BdH$_4$][PpH]	4.74
1	1	6	54.08	[BdPpH$_6$]/[BdH$_6$][Pp]	12.56	5.6	[BdPpH$_6$]/[BdH$_4$][PpH$_2$]	5.36
1	1	7	58.73	[BdPpH$_7$]/[BdH$_6$][PpH]	8.80	3.3	[BdPpH$_7$]/[BdH$_5$][PpH$_2$]	6.25
1	1	8	60.73	[BdPpH$_8$]/[BdH$_6$][PpH$_2$]	4.86	<2.0	[BdPpH$_8$]/[BdH$_6$][PpH$_2$]	4.86

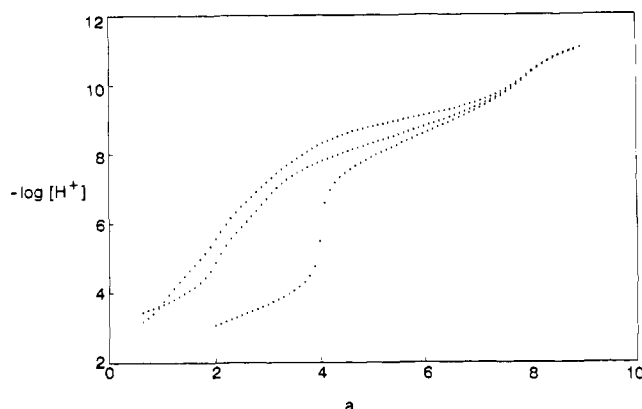[a] This work. $\sigma_{fit} = 0.0018$; 25.0 °C; $\mu = 0.100$ KCl.

Figure 2. Potentiometric equilibrium curves. Top: experimental solution containing 2.0×10^{-3} M OBISDIEN + 2.0×10^{-3} M pyrophosphate. Middle: calculated for above assuming no interaction. Bottom: experimental solution containing 2.0×10^{-3} M OBISDIEN alone. Conditions: $-\log[H^+]$ as a function of a, moles; 0.1 M KOH added per mole of ligand present at 25.0 °C; $\mu = 0.100$ M KCl.

kcal·mol^{-1}·deg^{-2} to describe both the cis and trans N—Cu—N bending constants. In this approach, the two pairs of trans nitrogens are distinguished in the calculation as the otherwise identical N3+ and N3T+ in the SYBYL notation, so as to allow the program to differentiate between ideal N—Cu—N angles that must be 90 or 180°. The ideal Cu—N—C bending constants were set at 0.008 kcal·mol^{-1}·deg^{-2}, with an ideal angle of 109.5°. The trial structures used for the calculations were the reported structures[2-4] for dicopper(II) complexes and also structures generated by using the BUILD facility of SYBYL. In order to try to generate further low energy structures, the structures generated were subjected to molecular dynamics runs on the DYNAMICS module of SYBYL. The dynamics runs were inspected for low energy structures, and these were subjected to energy minimization.

Repeating the energy minimization described in the Experimental Section established the "bowl-shaped" conformer in Figure 1 as being of uniquely low energy and potentially important in complexing short ligands such as F$^-$ or OH$^-$ as bridges between the two coppers. Numerous conformers with variable degrees of buckling of the ethereal bridge between the two copper—DIEN parts of the complex were found, and only the ones shown in Figure 1 are discussed here, as they are all of reasonably low energy. At the extreme end of the Cu to Cu separation is the "extended" conformer shown in Figure 1a, which has the maximum possible extension of the ethereal bridges and which is also of low energy. The ethereal bridges can be attached to the terminal nitrogens of each copper—DIEN end of each conformer so as to be axial or equatorial on the Cu(II)—DIEN complex chelate rings. Whether the attachment of the ethereal bridges to the nitrogen donors of the copper(II)—DIEN part of the complex is axial or equatorial does not much affect the Cu to Cu separation, but does affect the energy, and the orientation of the Coppers for coordination of bridging ligands. Thus, all the conformers in Figure 1 have equatorial attachment of the ethereal bridges to the nitrogens of the copper(II)—DIEN complex ends of the complex, which leads to lower energy. An alternative conformation for the extended conformer has axial attachment of the ethereal bridges to the copper(II)—DIEN complex ends, which does not affect

the Cu to Cu separation. This conformer has a low energy because of a better interaction with the ethereal bridges of OBISDIEN. However, the orientation of the copper(II)—DIEN ends of the complex is inappropriate for coordination of pyrophosphate, so that this conformer was not considered further here.

The Cu to Cu separations shown in Figure 1 were calculated with no bridging ligand present. Calculations were also carried out with a μ-hydroxo bridge in conformer c in Figure 1, a μ-phosphate bridge in conformer b, and a μ-pyrophosphate bridge in conformer a in Figure 1, to determine how well these fitted into the cavities. For these the constants were the same as used for nitrogen donors, but a shorter Cu—O ideal bond length of 1.97 Å gave satisfactory reproduction of the reported[3] μ-hydroxo-bridged structure.

Results and Discussion

Protonation Constants. Although the protonation constants of OBISDIEN, **1**, had been determined previously, it is important to redetermine these constants under the exact conditions of ionic medium and temperature used in the present investigation, while at the same time determining the precise working molecular weight of the ligand hydrobromide. The values of the successive log protonation constants thus obtained are 9.58, 8.89, 8.26, 7.64, 3.79, and 3.36, $\sigma_{fit} = 0.0012$ ($\mu = 0.100$ M KCl, 25.0 °C). In the supplementary material one can find the experimental titration curve as well as a detailed comparison of these values in relation to the literature data. The agreement with previous work is excellent with no systematic deviations apparent.

Pyrophosphate. Tetrasodium pyrophosphate was titrated after acidification, but only three protonations could be obtained from the data. Evidently, the fourth protonation is too weak to be detected at 0.002 M concentration by regular potentiometry. The experimentally determined values of the three log protonation constants of pyrophosphate are 8.40, 5.95, and 1.8 ($\sigma_{fit} = 0.0018$, $\mu = 0.100$ M KCl, 25.0 °C) and their comparison with literature values can be found in the supplementary material in Table S2. The protonation constants of pyrophosphate are sensitive to the medium chosen for maintaining the ionic strength. For this reason it was imperative to determine the protonation constants of pyrophosphate under the present equilibrium conditions.

Cu(II)—OBISDIEN Complexes. Copper(II)—OBISDIEN is known to form mononuclear, dinuclear, protonated, and unprotonated complexes of OBISDIEN.[1,20] These complexes were reinvestigated in order to determine the constants under the conditions of the present investigation and the results computed from the titration data are shown in Table 1. An experimental 1:1 ratio favors the formation of mononuclear Cu(II)—OBISDIEN complexes and a 2:1 experimental ratio of Cu^{2+}: OBISDIEN favors the formation of dinuclear complexes. However since there are considerable concentrations of dinuclear complexes in 1:1 systems and mononuclear complexes are present in 2:1 solutions, the mononuclear constants were
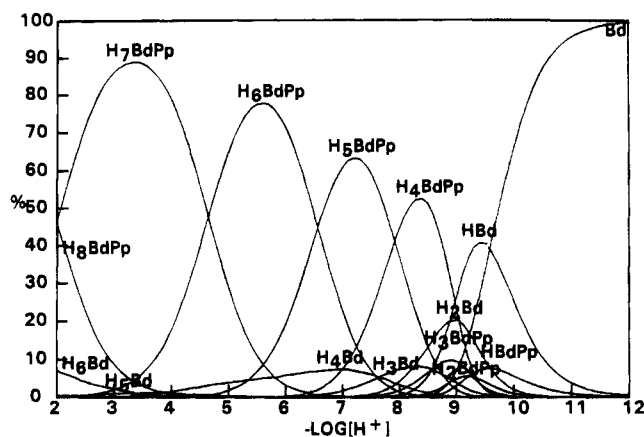
Figure 3. All OBISDIEN species present plotted resulting from the interaction of 2.0×10^{-3} M OBISDIEN with 2.0×10^{-3} M pyrophosphate as a function of $-\log[H^+]$ at 25.0 °C and $\mu = 0.100$ M KCl.

calculated from the 1:1 titration data while the dinuclear constants were calculated from the 2:1 Cu^{2+}:OBISDIEN data. These constants were systematically iteratively refined until a consistent set of log β's was obtained, satisfying both the 1:1 and 2:1 experimental curves. The results show no significant deviations between previous work and the present determination. The fact that there *are* differences underscores the necessity to determine all background equilibrium constants under the conditions of the analysis because their relative precision is important in assuring a high absolute accuracy for the measurements and computations in the recognition phase of the work.

Copper(II)—Pyrophosphate Complexes. The stability constants for the Cu(II)—pyrophosphate system have been determined in at least 18 publications,[20] and an examination of the species distribution curves based on these data shows that in the absence of other ligands only two formation constants could be of importance in this work: log $K_{ML} = 7.60$ and log $\beta_{MHL} = 12.87$. Two other equilibria would contribute at a very low level, log $\beta_{MH_2L} = 16.37$ and log $\beta_{ML_2} = 12.45$, and these thus were included for completeness into the refinement calculations. Attempts to redetermine these constants in this laboratory were complicated by the onset of precipitation of neutral salts formed from Cu^{2+} and pyrophosphate at lower pH and that of $Cu(OH)_2$ at and above p[H] 6.5. However, since copper(II) pyrophosphate species are expected to be negligible in the mixed ligand experiments, it was considered justifiable to use the literature values, and no further attempts were made to redetermine these constants.

OBISDIEN—Pyrophosphate System. The determination of the OBISDIEN recognition constants for pyrophosphate was made through the comparison of titration data of OBISDIEN with and without pyrophosphate. These are shown in Figure 2 and the computed results are given in Table 2. In the presence of pyrophosphate, the familiar OBISDIEN curve with its sharp break at $a = 2$ is transformed into a highly buffered featureless curve which differs considerably from the one calculated from the protonation constants alone, *i.e.* assuming no recognition. At high pH all three curves merge into a single one since all species are deprotonated under these conditions and there is no recognition.

From a species-distribution viewpoint shown in Figure 3, it is clear that the negatively charged oxygens on pyrophosphate

and the positively charged ammonium groups of OBISDIEN result in strong recognition. In fact, five host-guest species H_8-$BdPp^{4+}$—H_4BdPp are the major constituents below p[H] 9. A possible H-bonding scheme for H_4BdPp is illustrated in formula **2** in Chart 1. At higher p[H] where Bd is less protonated, the remaining H_3BdPp^-—H_1BdPp^{3-} species form at somewhat lower concentration, but they are not negligible. Whereas there is no precipitous drop in the values the stepwise constants in going from H_4BdPp to H_3BdPp^- (Table 2), the large drop in the actual concentrations of the H_3BdPp^- species is the result of the drop in protonation of Bd that occurs in the p[H] rnage 8—10. Figure 3 also shows that the pyrophosphate 4— anion has very high affinity for the hexaprotonated OBISDIEN species. However, at the p[H] at which H_6BdPp^{2+} is the main species, the principal forms of the host ligand and the guest are H_4Bd^{4+} and H_2Pp^{2-}, respectively, for which the binding constant is 5.36, as indicated in Table 2. As pyrophosphate becomes protonated its affinity for the hexaprotonated OBISDIEN species decreases.

The mode of binding of the various protonated forms of OBISDIEN is considered to involve multiple hydrogen bonds. Similar hydrogen bonding can be inferred from a study of bis-(ethylenediammonium) disphosphate where both the crystal structure and Raman spectra showed that the cohesion and stability of the bonding between the amine and the phosphate ion results from the N--H$\cdots$O bonds present.[21] The spermidinium ion, $[NH_3CH_2CH_2CH_2NH_2CH_2CH_2CH_2CH_2NH_3]^{3+}$, has also been studied for its binding with pyrophosphate, and its log formation constant with the tetraanion has been reported as 2.5.[22] The wide separations of ammonium groups makes this analog not very suitable for drawing inferences. However, it was found that the enthalpy change is very unfavorable, and that the stability derives from a positive entropy which supports the postulation of largely ionic interaction forces.

Cu(II)—OBISDIEN—Pyrophosphate System. In the absence of pyrophosphate, the 1:1 titration curve has an initial inflection at $a = 4$ indicating initial formation of CuH_2L^{4+} near p[H] 6. There is subsequent proton dissociation and the ultimate CuL^{2+} complex forms near p[H] 8. Likewise, the 2:1 M:L titration curve shows the initial formation of Cu_2L^{4+} with a break at $a = 6$ followed by μ-hydroxo complex formation from $a = 6$ to $a = 7$, followed finally by the formation of $Cu(OH)_2L$ from $a = 7$ to 8. The actual speciation includes several other minor species and considerable formation of 1:1 species in 2:1 systems and vice versa.

When pyrophosphate is present (Figure 4) two pairs of curves are obtained, for the 1:1:1 and 1:2:1 Bd:Cu:Pp systems respectively. For the 1:1 case the inflections at $a = 4$ and $a = 6$ are no longer there, while in the 2:1 Cu:L case there are new potential jumps at $a = 5$ and $a = 6$. Figure 4 also shows corresponding curves calculated on the assumption that the individual ligands and complexes with their own equilibrium constants are the sole determinants of the observed solution p[H]. The dramatic differences clearly show that there is considerable association between the various mononuclear and dinuclear species and pyrophosphate. Since these large differences occur throughout the accessible p[H] range, the data show that the interactions between the complexes formed and pyrophosphate must be high indeed.
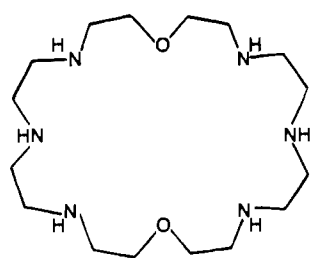
The experimental data plotted in Figure 4, taken with all the known background equilibrium constants obtained from the

(20) Smith, R. M.; Martell, A. E.; Motekaitis, R. J. *Critical Stability Constants Database*, Beta Version; NIST: Gaithersburg, MD, 1993.

(21) Kamoun, S.; Jouini, A.; Daoud, A. *J. Solid State Chem.* **1992**, 18.

(22) Labadi, I.; Janei, E.; Lahti, R.; Lonnberg, H. *Acta Chem. Scand.* **1991**, *45*, 1055.

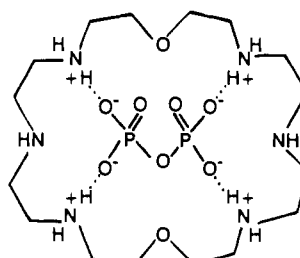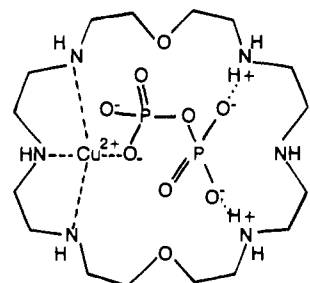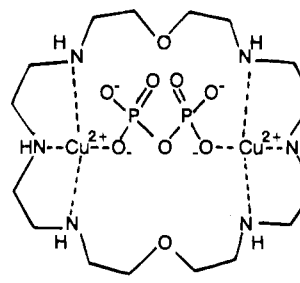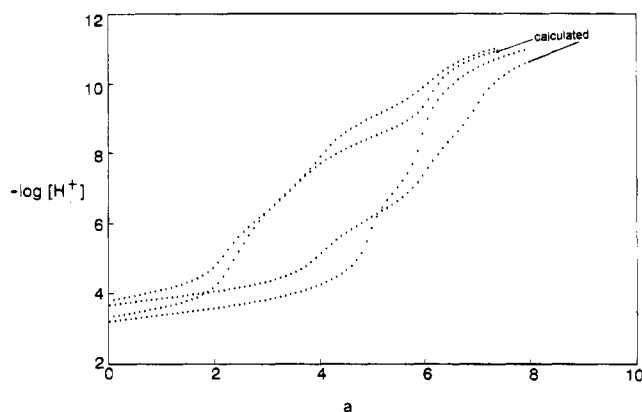**Chart 1**

1   The macrocyclic ligand OBISDIEN

2   Probable hydrogen bonding in H$_4$BdPp

3   Probable coordinate bonding in CuH$_2$BdPp

4   Probable coordinate bonding in Cu$_2$BdPp

Figure 4. Comparison of observed formation curves with theoretical curves calculated based on assumption of zero recognition for both 1:1:1 (top pair) and 1:2:1 Bd:Cu:Pp (bottom pair) systems. In both cases the experimental curve starts below, crosses over, and then finishes above the calculated one showing considerable recognition. Conditions: 2.0 × 10^{-3} M OBISDIEN + 2.0 × 10^{-3} M or 4.0 × 10^{-3} M Cu^{2+} + 2.0 × 10^{-3} M pyrophosphate; −log[H$^+$] as a function of moles of 0.1 M KOH added per mole of ligand present at 25.0 °C; μ = 0.100 M KCl.

Table 3. Overall Stability Constants for the Cu(II)−OBISDIEN−Pp System, (μ = 0.100 M KCl, 25.0 °C; Bd = L = OBISDIEN, Pp = Diphosphate, M = Cu^{2+}, H = H$^+$, OH = OH$^-$)

stoichiometry						stepwise
Bd	Cu	Pp	H	log β^a	stepwise quotient K	log K^a
1	1	1	0	19.07	[BdCuPp]/[BdCu][Pp]	2.86
1	1	1	1	28.72	[BdCuPpH]/[BdCuH][Pp]	4.71
1	1	1	2	38.02	[BdCuPpH$_2$]/[BdCuH$_2$][Pp]	6.25
1	1	1	3	45.14	[BdCuPpH$_3$]/[BdCuH$_3$][Pp]	9.93
1	1	1	4	51.18	[BdCuPpH$_4$]/[BdCuH$_3$][PpH]	7.57
1	1	1	5	54.79	[BdCuPpH$_5$]/[BdCuH$_3$][PpH$_2$]	5.23
1	2	1	0	35.50	[BdCu$_2$Pp]/[BdCu$_2$][Pp]	8.50
1	2	1	1	42.59	[BdCu$_2$PpH]/[BdCu$_2$][PpH]	7.19
1	2	1	2	46.99	[BdCu$_2$PpH$_2$]/[BdCu$_2$][PpH$_2$]	5.65
1	2	1	−1	25.28	[BdCu$_2$Pp(OH)]/[BdCu$_2$(OH)][Pp]	4.66

^{a} This work. σ_{fit} = 0.0054 (1:1:1); σ_{fit} = 0.0043 (Bd:Cu^{2+}:Pp = 1:2:1).

previously investigated systems, were used in the refinement of constants for the Cu(II)−OBISDIEN−pyrophosphate system. The data show that 10 species containing Cu^{2+}, OBISDIEN, and pyrophosphate are present in solution, and their overall and stepwise formation constants are given in Table 3.

The species distribution diagram of the 1:1:1 system shown in Figure 5 reveals that in the p[H] range 2−12 there are 10 species containing pyrophosphate bound to coordinated Cu(II) and/or protonated amino groups. None of the species exceed about 50%, nor are they minor. The more important mononuclear species are CuH$_4$BdPp^{2+} at p[H] 5−6, CuH$_3$BdPp$^+$ at p[H] 6−7 and CuH$_2$BdPp at p[H] 8. The probable coordination sites of the host−guest complex is illustrated in formula **3**, CuH$_2$-BdPp, which indicates the pyrophosphate anion coordinated to the Cu(II) and hydrogen bonded to the protonated nitrogens of OBISDIEN. Also, even though the ratio of metal to ligand is

1:1, pyrophosphate appears to stabilize several dinuclear complexes, including the dicopper μ-hydroxo−μ-pyrophosphato complex.

As the relative copper(II) concentration is doubled, the species distribution diagram (Figure 6) becomes simpler in that above pH 4 only the dinuclear copper complexes are now important species. The major complexes are Cu$_2$HBdPp$^+$, Cu$_2$BdPp, **4**, and Cu$_2$(OH)BdPp$^-$.

The affinity of pyrophosphate for Cu(II)−OBISDIEN complexes increases as the number of protons in OBISDIEN increases. When OBISDIEN is fully protonated, the pyrophosphate begins to get protonated as the p[H] is lowered further. The affinity of protonated pyrophosphate species for OBISDIEN decreases with the number of protons attached to the pyrophosphate.

Nothing could be said with absolute certainty about the microscopic details of each species, but reasonable arguments could be gleaned from previous studies, stoichiometries, relative sizes of the stepwise constants, and possibly molecular mechanics predictions. The species CuH$_5$BdPp^{3+} and CuH$_4$BdPp^{2+} no doubt have a CuH$_3$Bd^{5+} core and a diprotonated or monopro-
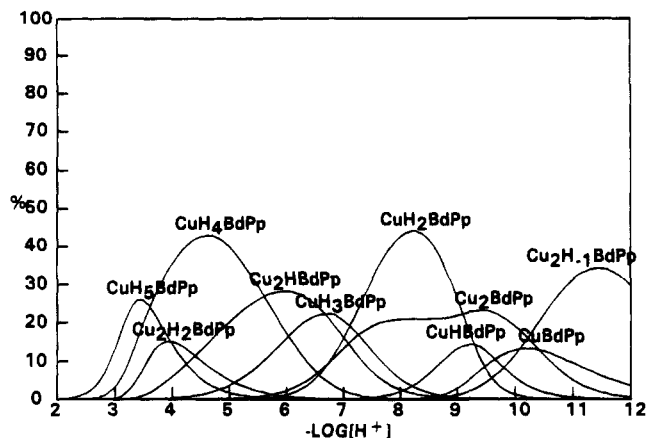
Figure 5. Species distribution resulting from a 1:1:1 solution at 2.0 × 10^{-3} M each of OBISDIEN, Cu^{2+}, and pyrophosphate, at 25.0 °C and $\mu = 0.100$ KCl. Only the ternary pyrophosphate-containing species are shown.
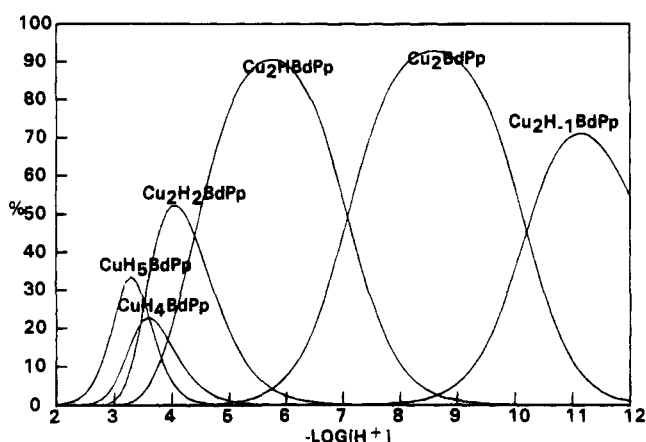

Figure 6. Species distribution resulting from a 1:2:1 solution at 2.0 × 10^{-3} M each of OBISDIEN and pyrophosphate, and 4.0 × 10^{-3} M Cu^{2+} at 25.0 °C, $\mu = 0.100$ M KCl. Only the ternary pyrophosphate-containing species are shown.

tonated pyrophosphate bridging the Cu^{2+} center and the positive protonated sites. Likewise, both of the protonated dinuclear complexes probably involve a bridging protonated pyrophosphate. The remaining mononuclear complexes have the tetranegative pyrophosphate anion bridging the dipositive copper ion and the protonated amino groups of the ligand.

A comparison of the stepwise formation constants of Cu_2-BdPp and CuH_2BdPp, both of which are neutral, reveals that the dinuclear species, Cu_2Bd, shows stronger binding for pyrophosphate by 2.25 log units. However, a comparison of pyrophosphate binding by Cu_2Bd^{4+} with CuH_3Bd^{5+}, shows that the binding constant of the mononuclear complex is higher by 1.43 log units. One might attribute these observations to more than a simple electrostatic effect, since in CuH_3Bd^{5+}, the close proximity of three positively charged ammonium groups has an organizing effect on the ligand in order to achieve a better fit than in Cu_2Bd^{4+} where ligand flexibility is lost by formation of the metal complex. Also, in the complex CuH_2Bd^{4+} the protonated amines are most likely far apart initially and thus upon addition of pyrophosphate energy is expended to rearrange the conformation to that of the species formed, CuH_2BdPp.

Molecular Mechanics Calculations. The MM calculations reproduced the known[2-4] structures of dicopper(II) complexes of OBISDIEN reasonably well. What was important, however, is the insight obtained that the OBISDIEN dicopper(II) complex is quite flexible, and is able to produce complexes of low energy
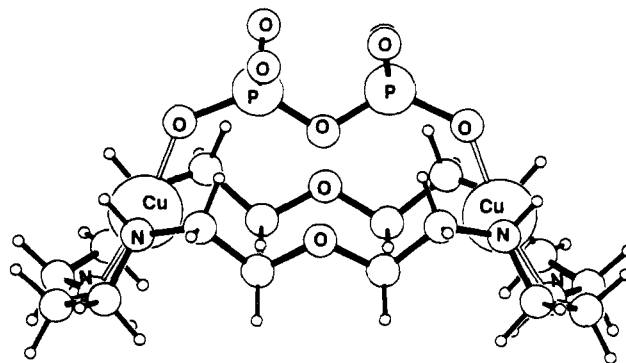
Figure 7. Probable structure of the pyrophosphate complex of dicopper(II) OBISDIEN, generated by molecular mechanics calculation using the SYBYL program.[19] The receptor Cu(II)–OBISDIEN was energy minimized first, and then pyrophosphate was docked onto the receptor and the resulting complex reminimized.

Table 4. Energies of Some Conformers of Complexes of the Dicopper(II) Complex of BISDIEN Calculated by Molecular Mechanics[a]

conformer[b]	energy[c]	Cu--Cu separation[d]	bridging ligands
bowl-shaped	10.29	4.27	none
bowl-shaped	21.32	3.58	μ-hydroxo
bowl-shaped	25.06	3.68	μ-hydroxo plus μ-perchlorato
observed[3]	14.73	4.27	none
observed[3]	22.05	3.53	μ-hydroxo
observed[3]	22.09	3.53	μ-hydroxo plus μ-perchlorato
intermediate	20.47	5.54	none
intermediate	19.01	5.55	μ-phosphato
extended	15.83	7.31	none
extended	20.20	7.08	μ-pyrophosphato

[a] Strain energies calculated using the program SYBYL[19] as described in the text. [b] The conformers are shown in Figures 1 and 8. [c] Energy in kcal·mol^{-1}. [d] Distance in Å.

with varying Cu to Cu separations, as shown in Figure 1. This means that the complex should be able to accommodate a range of μ-bridging ligands with sizes varying from F^- or OH^- at the short end of the range (Cu--Cu = 4.27 Å) to pyrophosphate at the long end of the range (Cu--Cu = 7.31 Å). A further insight obtained in the calculations with a bridging μ-hydroxo or bridging μ-pyrophosphate is that in general the bridging ligands are too bulky to lie between the ethereal bridges of the complex. As seen in the structures generated for these complexes (Figure 7 shows the pyrophosphate result) the ligands always lie above or below the ethereal bridges. The hydroxo bridge does appear[3] to hydrogen bond to the ethereal oxygens of the bridge, although these hydrogen bonds appear to be rather long (2.99 Å) and may therefore be of limited energetic importance. The bowl-shaped conformer in Figure 1c has a Cu to Cu separation that is actually a little too long for accomodating hydroxo or fluoro bridges. The Cu--Cu separation is pulled in from 4.27 Å with no bridge present to 3.58 Å with a μ-hydroxo bridge present. This pulling together of the two coppers causes the strain energy of the bowl-shaped conformer to rise quite considerably (Table 4).

The bowl-shaped conformer seen in Figure 1c is similar to that found in the μ-hydroxo bridged dicopper(II)–OBISDIEN complex reported by Coughlin and Lippard,[3] except that the central nitrogen on each end of the complex is inverted in the MM generated structure compared to the observed[3] structure. The reported structure thus has axial attachment of the ethereal bridges to the nitrogens of the Cu(II) DIEN ends of the complex, accounting for its higher energy than the MM generated bowl shaped structure. The bowl-shaped structure was generated

using model building coupled with repeated dynamics runs, followed by minimization, and is 4.5 kcal·mol^{-1} lower in energy than the reported structure in the absence of a bridging ligand. The Cu to Cu separation is identical in the reported[3] and MM generated bowl-shaped structure. Addition of a bridging hydroxide results in very similar energies for the bowl-shaped and observed conformers. The reported structure has a bridging perchlorate group coordinated to the axial sites of the copper-(II) atoms. It appears that the observed structure is adopted because this keeps the hydrogens on the ethylene groups betweeen the nitrogen donors of the ligand away from the bridging perchlorate group. This can be demonstrated by adding bridging perchlorate groups, which results in an energy some 3 kcal·mol^{-1} higher for the bowl-shaped than the observed structure (Table 4). It is interesting to note that the bowl-shaped conformer seen in Figure 1c is identical to that found[4] for the similar dicopper(II) 24-aneN$_2$O$_6$ complex with an end-on bridging μ-azide between the two copper atoms. Here there are also two bridging ligands between the two copper atoms, but these are both coordinated in an end on fashion (-κN:κN-) which gives very little steric bulk close in to the ligand, thus favoring the bowl-shaped conformer.

For bridging ligands of intermediate length, such as the bridging imidazole group reported,[2] rather irregular conformations are observed[2-4] for the OBISDIEN complexes. MM calculations with the observed structure[2] with an imidazolate bridge show it to be of rather high strain energy in the absence of bridging ligands. A structure of intermediate Cu--Cu

separation seen in Figure 1b is of fairly low energy, and allows bridging of ligands of intermediate length. This structure was observed by Lehn et al.[4] with bridging azides coordinated lengthways between the coppers. MM calculations also show this structure to be of high energy in the absence of bridging ligands, but it is very well suited to the coordination of a ligand such as phosphate (Table 4), with a relatively low energy structure resulting.

The MM calculations make the point that the OBISDIEN ligand can assume different conformations in its dicopper(II) complexes, and so is able to accomodate a variety of lengths in bridging ligands held between the two coppers. Future studies will be directed at the effects on structure and stability of more rigid bridges than considered here, such as those having a furan in place of the ethereal oxygen and its two attached methylenes in the bridge.

Supplementary Material Available: Table S1 contains protonation constants of the OBISDIEN system calculated from the titration results shown as the upper curve in Figure S1. The results are given in Table 1 together with those previously measured. Table S2 contains the overall and stepwise protonation constants of pyrophosphate (3 pages). Ordering information is given on any current masthead page.

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