unambiguously established by the synthesis of **D** starting with the monocyclic precursor **2b**.

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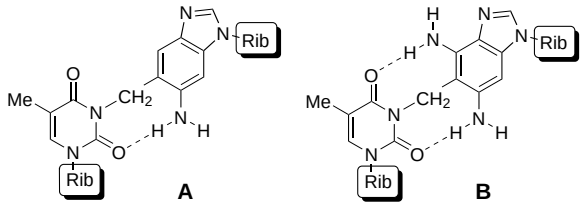
[1] T. G. Minehan, Y. Kishi, *Angew. Chem.* **1999**, *111*, 972; *Angew. Chem. Int. Ed.* **1999**, *38*, 923.
[2] Tolyporphin A *O*,*O*-diacetate was prepared ($Ac_2O$, pyridine, RT) from natural (+)-tolyporphin A.[3]
[3] M. R. Prinsep, F. R. Caplan, R. E. Moore, G. M. L. Patterson, C. D. Smith, *J. Am. Chem. Soc.* **1992**, *114*, 385.
[4] The numbering according to the proposed structure **1a** is adopted here.
[5] Eight additional tolyporphins have been isolated from the cyanophyte microalga: M. R. Prinsep, G. M. L. Patterson, L. K. Larsen, C. D. Smith, *Tetrahedron* **1995**, *51*, 10523.
[6] The $^1H-^1H$ NOESY and $^1H-^1H$ ROESY data were identical for each of the individual compounds studied. We chose to focus on the $^1H-^1H$ NOESY data because it displayed a better signal-to-noise ratio.
[7] The $^1H$ NMR spectra for the synthetic and natural tolyporphin A *O*,*O*-diacetates were shown to be concentration-independent in $C_6D_6$.

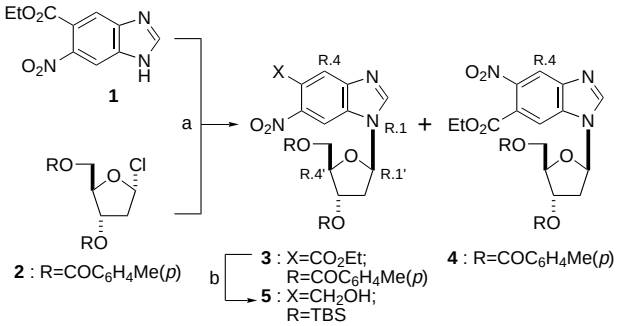
## Covalently Cross-Linked Watson – Crick Base Pair Models**

Xiaoxin Qiao and Yoshito Kishi*

The concept of covalently linked cross sections with molecular architecture similar to Watson – Crick hydrogen-bonded base pairs was introduced by Leonard in the mid-1980s.[1] Since then, several types of covalently linked systems have been developed and used for a variety of purposes.[2] In our view, base pairs linked with a methylene bridge such as **A** and **B** may add some new aspects to the chemistry of covalently linked nucleosides/nucleotides. These include: 1) only Watson – Crick and reversed Watson – Crick base pairings are possible for these models,[15] and 2) conformational flexibility is expected to be retained along the bridging methylene bonds, in addition to their expected increased chemical stability. Evidently, there is concern about such models; introduction of the $CH_2$ bridge would not allow the two bases to be in the same plane, and consequently models such as **A** and **B** might not properly mimic the Watson – Crick base pairs. However, molecular mechanics calculations have suggested that the deformation caused by the introduction of the methylene bridge to a double-stranded oligomer may be insignificant.[3] Herein we report a general synthetic route to the type **A** base pairs and the elucidation of their structures in both solid and solution states, thereby demonstrating that they indeed possess (some of) the structural characteristics of Watson – Crick hydrogen-bonded base pairs.




Ethyl 6-nitro-5-benzimidazole carboxylate (**1**; m.p. 154 – 157 °C (EtOH)) was readily prepared from commercially available 5-benzimidazole carboxylic acid in two steps (1. EtOH/cat. $H_2SO_4$/reflux and 2. fuming $HNO_3/H_2SO_4$/50 °C) in 85 % overall yield. Under phase-transfer conditions,[4] **1** was coupled with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentosyl chloride (**2**)[5] to give a 1:1 mixture of N1- and N3-glycosides **3** and **4**, which were readily separated by silica gel column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$/EtOAc (4/1)) in 95 % combined yield (Scheme 1). A better than 20:1




Scheme 1. Reagents and conditions. a) KOH/[18]crown-6/MeCN/RT; b) 1. $K_2CO_3$/EtOH/RT; 2. TBS-Cl/imidazole/DMF/RT; 3. NaOH/*t*BuOH/RT; 4. $ClCO_2Et/Et_3N$/THF/0 °C; 5. $NaBH_4$/EtOH/0 °C. TBS = *tert*-butyldimethylsilyl.

$\beta$ selectivity was observed for the N1- and N3-glycosides. The structures of **3** and **4** were established by NOESY experiments. In **3**, the R.1′-H exhibited strong crosspeaks with R.4′-H, R.2-H, and the proton *ortho* to the nitro group (R.7-H), respectively. In **4**, the R.1′-H showed strong crosspeaks with R.4′-H, R.2-H, and the proton *ortho* to the carboethoxy group (R.7-H), respectively.[6]

The N1-glycoside **3** was converted to the primary alcohol **5** in five steps in 55 % overall yield (Scheme 1). After mesylation, **5** was coupled with 3′,5′-di-*O*-(*tert*-butyldimethyl)silylthymidine (**6**)[7] to give the $CH_2$-linked product **7** in nearly quantitative yield (Scheme 2). Alternatively, the coupling of **5** with **6** to yield **7** was achieved in one step in 96 % yield under the Mitsunobu conditions.[8] Reduction of the nitro group of **7**,

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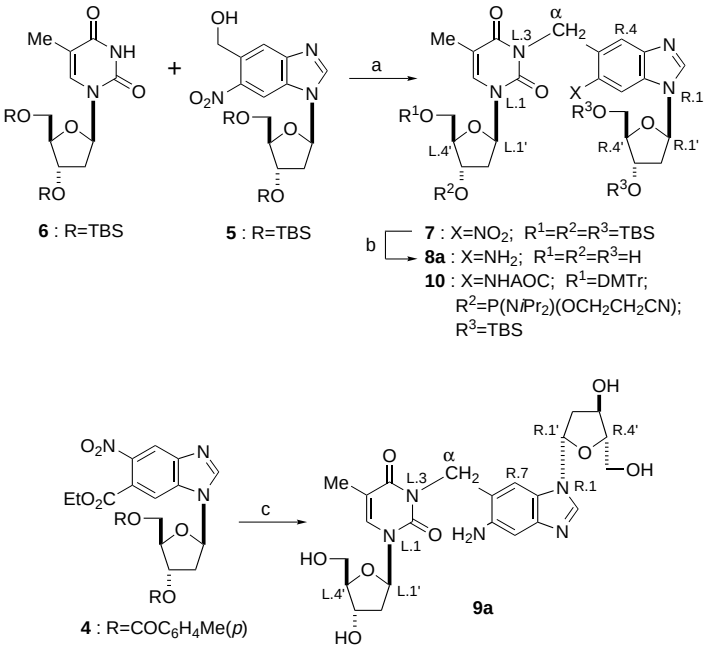
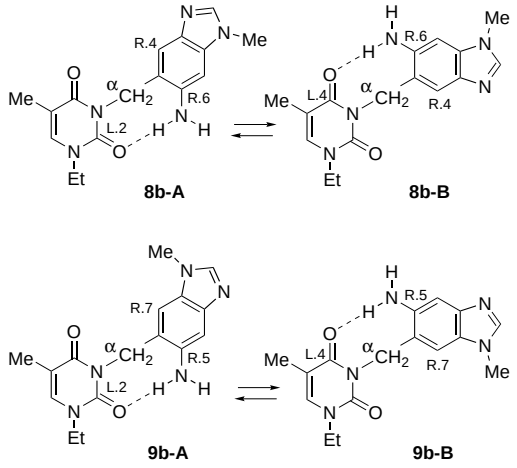



Scheme 2. Reagents and conditions. a) 1. Mesylation of **5**: $MsCl/Et_3N/CH_2Cl_2/0\,^{\circ}C$; 2. $K_2CO_3$/DMSO/RT or a) DEAD/$PPh_3$/THF/0 °C → RT; b) 1. $SnCl_2$/EtOH/RT → 70 °C; 2. TBAF/THF/RT; c) follow the steps shown under b in Scheme 1 and then the steps shown under a and b in this scheme. For the synthetic sequence for **10**, see reference [13]. AOC = allyloxycarbonyl, DEAD = diethylazodicarboxylate, DMTr = 4,4′-dimethoxytriphenylmethyl, Ms = methanesulfonyl, TBAF = tetrabutylammonium fluoride.

followed by *tert*-butyldimethylsilyl (TBS) deprotection, furnished the $CH_2$-linked **8a** (m.p. 215–216 °C ($CF_3CH_2OH$/MeOH)) in 65% overall yield from **7**. Using the same sequence of reactions, the $CH_2$-linked **9a** (m.p. >230 °C (95% EtOH)) was obtained from the N3-glycoside **4**.

Compounds **8a** and **9a** were recrystallized from trifluoroethanol/methanol and 95% methanol, respectively, to give fine needles. However, all efforts to grow a single crystal suitable for X-ray structure analysis met with no success. Therefore, we prepared[9] the corresponding $CH_2$-linked base pairs **8b** (m.p. 215–217 °C (EtOAc/EtOH)) and **9b** (m.p. >




230 °C (EtOAc/EtOH)) and then subjected them to X-ray analyses (Figure 1).[10] The X-ray analyses revealed interesting structural aspects. First, the $CH_2$-linked base pair **8b** illus-

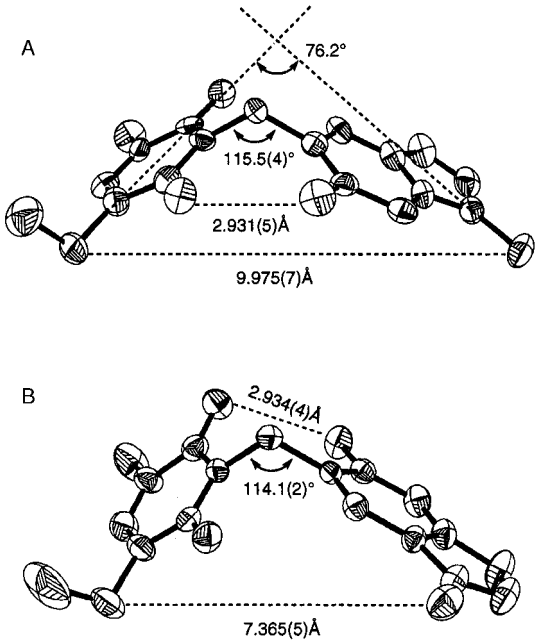



Figure 1. X-Ray structures of **8b** (A) and **9b** (B).

trates an excellent structural similarity to C–G and A–T base pairs; the X-ray structure analysis of **8b** gives the R.1′–L.1′ distance of 9.975(7) Å and an angle of 76.2° (see Figure 1), compared with a C1′–C1′ distance of 10.60 ± 0.15 Å and an angle of 68 ± 2° for C–G and A–T base pairs.[11] Superposition of the X-ray structure of **8b** over C–G and A–T base pairs illustrates that the areas that they occupy are nearly identical (Figure 2). Second, a hydrogen bond is

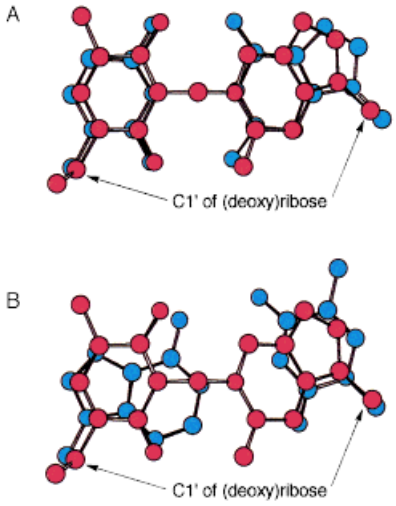



Figure 2. Superposition of the X-ray structure of **8b** (red) over C–G (A; blue) and A–T (B; blue) base pairs.

clearly recognizable between the L.2 C=O and the R.6 N–H group, that is, the distance between the oxygen atom at L.2 and the nitrogen atom at R.6 is 2.931 Å. However, there is no intermolecular hydrogen bond recognizable in the crystal packing of **8b**, that is, there is no Hoogsteen or wobble pairing present even in the solid state. Third, the $sp^3$-bridging displayed

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a substantially widened bond angle (115.5(4)°). Fourth, contrary to the **8b** series, in the **9b** series the R.5 amino group is hydrogen-bonded with the carbonyl oxygen atom at L.4. Thus, like the **8b** series, both the R.1-Me group and the L.1-Et group remain on the same side of the molecule in the **9b** series. However, the R.1′–L.1′ distance of 7.365(5) Å and an angle of 43.5° does not allow **9b** to occupy an area similar to that occupied by a C–G or A–T pair. Once again, there is no intermolecular hydrogen bond detected for **9b**.

The rotational freedom along the $CH_2$ bridge was studied by temperature-dependent $^1$H NMR spectroscopy (Figure 3). Most significantly, the proton signals of the $CH_2$ bridge of **8b** were observed as a sharp singlet at room temperature but split

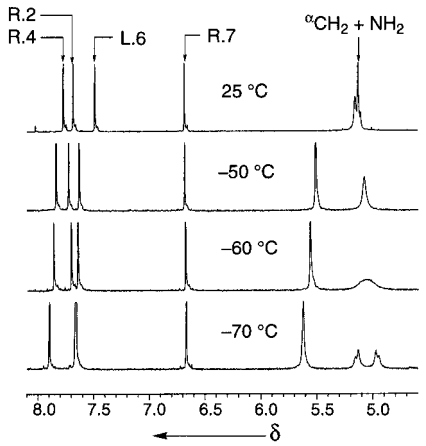
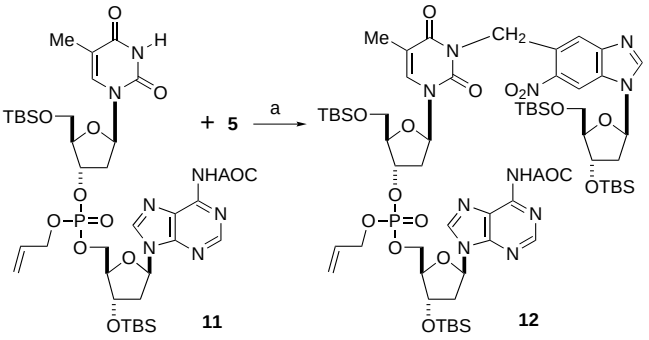



Figure 3. Variable-temperature $^1$H NMR spectra (500 MHz, in [$D_6$]acetone; $\delta = 4.6-8.2$ region) of **8b**. The indicated chemical shift assignments represent those at room temperature. However, the chemical shifts of R.2 and R.4 protons are switched with each other at −50 °C.

into an AB quartet at about −70 °C; the coalescent temperature of about −60 °C suggests the energy barrier for the rotation to be about 10 kcal mol$^{-1}$.[12] The trend in chemical shift change observed for the $NH_2$ protons indicated their involvement in hydrogen-bonding interactions. Although there is no experimental evidence available at present, it is tempting to suggest the preferred solution conformer to be **8b-A**, corresponding to the conformer observed in the solid state. The exact same phenomenon was observed for **9b**, with the energy barrier for the rotation being again about 10 kcal mol$^{-1}$. Once again, the preferred solution conformer at −70 °C probably corresponds to the solid-state conformer **9b-B**. Furthermore, the nucleotides **8a** and **9a** exhibited structural characteristics parallel to **8b** and **9b**, respectively.

The structural characteristics observed for covalently cross-linked base pairs such as **8** and **9** may suggest their interesting and unique potential. It is worth commenting on the flexibility of the current synthetic route. As the base-induced coupling of **5** is effective for the thymidines with R = Ac, benzoyl (Bz), *tert*-butyldiphenylsilyl (TBDPS), triethylsilyl (TES), tetrahydropyranyl (THP) in **6**, or even with unprotected thymidine (R = H in **6**), it should be feasible to synthesize the $CH_2$-linked base pairs bearing the left-side 2-deoxyribose moiety protected differentially from the right-side portion. Indeed, the $CH_2$-linked base pair **10** (Scheme 2) was obtained straightforwardly[13] and should be a useful precursor for preparation of oligonucleotides containing the covalently linked base pair. Alternatively, one could couple an oligonucleotide with an oligonucleotide through methylene bridge formation to obtain a double-stranded oligomer. In order to test the feasibility of this approach, the dinucleotide **11**[14] was coupled with mesylated **5**, to furnish **12** in excellent yield (Scheme 3).




Scheme 3. Reagents and conditions. a) 1. **5**: MsCl/$Et_3N$/$CH_2Cl_2$/0 °C; 2. $K_2CO_3$/DMSO/RT.

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**Keywords:** DNA structures · nucleosides · nucleotides · Watson–Crick base pairs

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[3] The fifth base pair in a self-conplementary, double-stranded nanomer [d(tgactgact)$_2$] was replaced with the covalently cross-linked base pair **B**, and the resulting nanomer [d(tgacXgact)$_2$] ($X_2$ = **B**) was subjected to an energy minimization (MacroModel, force field: Amber), showing that the energy-minimized [d(tgacXgact)$_2$] retained B-form without losing any one of 22 Watson–Crick type hydrogen bonds. However, slight deformations were noted for the base pairs and ribose-backbones adjacent to the base pair **B**.

[4] F. Seela, W. Bourgeois, *Synthesis* **1989**, 912.

[5] C. C. Bhat in *Synthetic Procedures in Nucleic Acid Chemistry*, *Vol. 1* (Eds.: W. W. Zorbach, R. S. Tipson), Wiley, **1968**, p. 521.

[6] For the numberings adopted in this paper, see structures **3**, **8a**, and **9a**. "R." and "L." refer to the right- and left-side rings, respectively.

[7] M. M. Alauddin, P. S. Conti, *Tetrahedron* **1994**, *50*, 1699.

[8] For a review on Mitsunobu reactions, see: O. Mitsunobu, *Synthesis* **1981**, 1.

[9] Compounds **8b** and **9b** were prepared by functionalization of ethyl 1-methyl-6-nitro-5-benzimidazole carboxylate or ethyl 1-methyl-5-nitro-6-benzimidazole carboxylate (1. NaOH/*t*BuOH/RT; 2. $ClCO_2Et$/

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$Et_3N$/THF/0 °C; 3. $NaBH_4$/EtOH/0 °C; 4. MsCl/$Et_3N$/$CH_2Cl_2$/0 °C), followed by coupling ($K_2CO_3$/DMSO/RT) with 1-ethylthymine.

[10] The L.1-Me base pairs corresponding to **8b** and **9b** were also subjected to X-ray structure analyses; their structural characteristics were found to be very similar to those observed for **8b** and **9b**, respectively. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-114659 (**8b**) and CCDC-114660 (**9b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[11] For example, see: *Nucleic Acids in Chemistry and Biology,* 2nd ed. (Eds.: G. M. Blackburn, M. J. Gait), Oxford University Press, Oxford, **1996**, p. 21.

[12] For reviews on dynamic NMR spectroscopy, see: E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 502, and references therein.

[13] This transformation was carried out in six steps: 1. coupling ($K_2CO_3$/DMSO/RT) of **6** (R = Ac) with mesylated **5**; 2. $SnCl_2$/EtOH/RT → 70 °C; 3. AOC-OBT/py/RT; 4. $NH_3$/MeOH/RT; 5. DMTr-Cl/$AgNO_3$/py/THF/RT; 6. ClP(N*i*Pr$_2$)(OCH$_2$CH$_2$CN)/NE*t*i Pr$_2$/$CH_2Cl_2$/RT. AOC = allyloxycarbonyl, BT = benzotriazole.

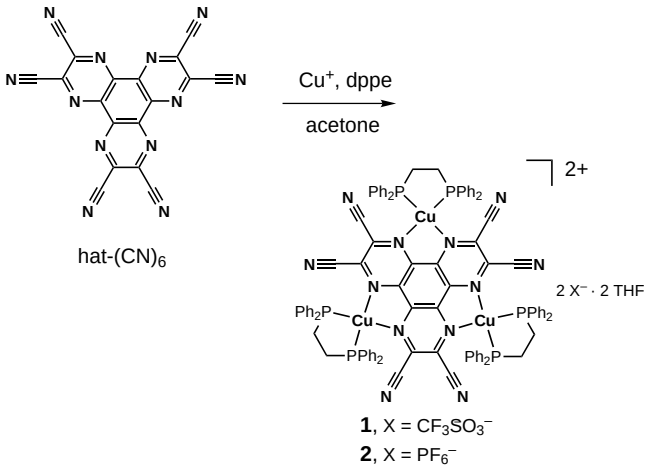
[14] The dinucleotide **11** was prepared from 5′-*O*-(*tert*-butyldimethylsilyl)thymidine 3′-*O*-(allyl-*N*,*N*-diisopropylphosphoramidite) and 3′-*O*-*tert*-butyldimethylsilyl-$N^6$-alloxycarbonyl-2′-deoxyadenosine in two steps: 1. 1*H*-tetrazole/MeCN/RT; 2. *t*BuCO$_2$H/$CH_2Cl_2$/RT, and then coupled ($K_2CO_3$/DMSO/RT) with mesylated **5**.

[15] Note added in proof (February 11, 1999): In the sense of primary hydrogen-bonding base pairing, only Watson–Crick and reversed Watson–Crick base pairings are possible for models **A** and **B**. However, it should be noted that Hoogsteen triplets such as T–AT and T–GC are envisioned for model **B**, but not for model **A**.

# A New Anion-Trapping Radical Host, $[(Cu\text{-}dppe)_3\{hat\text{-}(CN)_6\}]^{2+}$ **

Takashi Okubo, Susumu Kitagawa,* Mitsuru Kondo, Hiroyuki Matsuzaka, and Tomohiko Ishii

Hexaazatriphenylene hexacarbonitrile, hat-$(CN)_6$, is expected to act as a unique multidentate ligand because the characteristic electron-deficient heterocyclic core has low-lying degenerate π* orbitals. To date several metal complexes containing hat derivatives have been reported;[1, 2] however, preparation of metal complexes containing the hat-$(CN)_6$ ligand is extremely difficult because the coordination ability of the aromatic nitrogen atoms in hat-$(CN)_6$ drastically decreases due to the presence of the electron-withdrawing cyano groups. The one-electron reduction of hat-$(CN)_6$ efficiently enhances its coordinating ability, and we have been able to demonstrate this by isolating the first transition metal complexes **1** and **2** (dppe = 1,2-bis(diphenylphosphanyl)ethane), which exhibit anion-trapping behavior both in the solid state and in solution (Scheme 1).




Scheme 1. Synthesis of **1** and **2**.

Complexes **1** and **2** were prepared in a one-pot reaction of a copper(I) source ($[\{Cu(CF_3SO_3)\}_2(benzene)]$ (**1**) or $[Cu(CH_3CN)_4]PF_6$ (**2**)), hat-$(CN)_6$, and dppe in acetone. The hat-$(CN)_6$ ligand is reduced by the copper(I) ion in the solution, affording the corresponding $[hat\text{-}(CN)_6]^-$ ion. This anion can also be prepared electrolytically. The crystal structures of **1** and **2** have been determined by X-ray crystallography.[3]

The cation in **1** has a trinuclear structure in which the unique sixdentate anion radical ligand $[hat\text{-}(CN)_6]^{\bullet-}$ coordinates to three Cu-dppe fragments (Figure 1). A similar

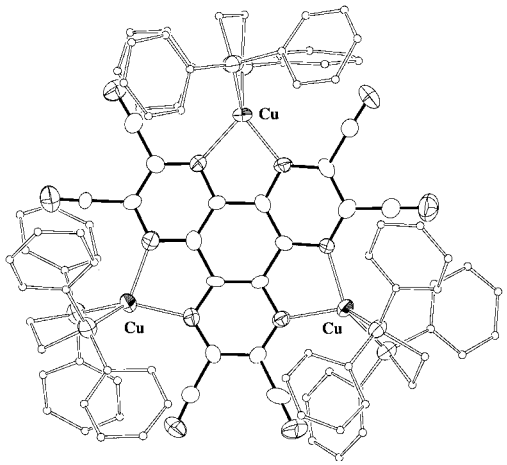



Figure 1. ORTEP view of the cationic moiety of **1** with thermal ellipsoids at 50 % level for Cu, P, C, and N atoms. All the hydrogen atoms are omitted for clarity. Ellipsoids of the carbon atoms in phenyl groups have been arbitrarily reduced for clarity.

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