In conclusion, we have discovered a molecule whose reactivity and molecular parameters led us to propose that it is a Hückel 10-π electron "bond-no-bond" resonance heteroaromatic singlet [no ESR signal (limit 1 spin/3 000 000 molecules) either in solution or in the solid state] trimethylenemethane outlined above.

In view of the fact that the disulfide linkage exhibits normal electrochemical properties one can expect that a large family of organic and transition-metal-derived compounds are preparable. We are actively pursuing this aspect as well as other chemistry[6] of this molecule.

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Supplementary Material Available: Complete listings of bond lengths and bond angles and anisotropic temperature factors as well as positional parameters and synthetic details (7 pages). Ordering information is given on any current masthead page.

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(16) The relevant parameters (italics, neutral TCNQ[13]) are as follows: C-N, 1.148 (6) versus *1.141*; exocyclic C=C, 1.372 (6) versus *1.374*; ring C-C, 1.446 (6) versus *1.446*; ring C-C, 1.455 (6) versus *1.450*; endocyclic C=C, 1.343 (6) versus *1.346*.

Molecular Recognition of Biologically Interesting Substrates: Synthesis of an Artificial Receptor for Barbiturates Employing Six Hydrogen Bonds[1]

Suk-Kyu Chang[2] and Andrew D. Hamilton*

Department of Chemistry, Princeton University
Princeton, New Jersey 08544

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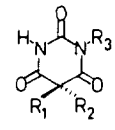
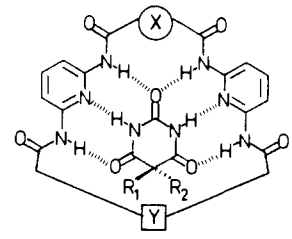
The role of hydrogen bonding in molecular recognition has been the focus of much recent attention.[3,4] In the design of artificial receptor molecules, the incorporation of several inwardly facing hydrogen bonding groups into a cleft[5] or cavity[6] of defined geometry should lead to strong and selective binding to those substrates showing complementary shape and H-bonding characteristics.[7] We have recently used this strategy to design receptors for thymine[8] involving three hydrogen bonds plus a stacking interaction.[9] In this paper we report the recognition and strong binding of barbiturate derivatives by a macrocyclic receptor containing *six* inwardly facing hydrogen bonds.

The families of drugs derived from barbituric acid **1a** are attractive targets for molecular recognition studies due to their widespread clinical use as sedatives[10] and anticonvulsants[11] and the range of derivatives available. Our approach to the recognition of barbiturates exploits the triple hydrogen bond complementarity between 2,6-diamidopyridines and imides.[9,12] Incorporation of two 2,6-diamidopyridine units into a macrocyclic structure (e.g., **2**) will permit the complexation of the six accessible hydrogen-



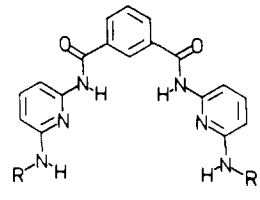


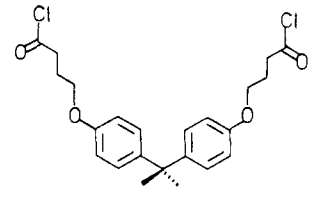
1a; $R_1 = R_2 = R_3 = H$
1b; $R_1 = R_2 = Et$, $R_3 = H$
1c; $R_1 = Et$, $R_2 = Ph$, $R_3 = H$
1d; $R_1 = Et$, $R_2 = Ph$, $R_3 = CH_3$
(racemic)

2

bonding groups in 5,5-disubstituted barbiturates (e.g., barbital, **1b**). Suitable choice of spacer Y may allow a secondary recognition of the substituents in the 5,5-positions. Molecular modeling studies suggested that an isophthaloyl group (as X in **2**) would provide the necessary organization and rigidity to form the hexadentate binding site and that a diphenylmethane derivative (as Y in **2**) would accommodate the 5,5-ethyl groups of barbital.

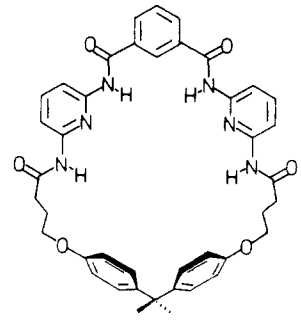
Reaction of isophthaloyl dichloride with an excess of 2,6-diaminopyridine (THF, Et_3N) gave diamine **3** in 79% yield. High dilution coupling of **3** and acid chloride **4** (THF, Et_3N) provided,





3; R = H
6; $R = CO(CH_2)_2CH_3$

4



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after alumina chromatography (CH_2Cl_2, MeOH) and crystallization from THF-heptane, macrocyclic tetraamide **5** in 12% yield.[13]

Complex formation between **5** or acycle **6** and various barbiturates was followed by ^1H NMR. For example, addition of 1 equiv of barbital **1b** to a $CDCl_3$ solution of **5** caused large downfield shifts of the host amide (1.65 and 1.63 ppm) and guest imide (4.38 ppm) proton resonances indicating the formation of

(1) This paper is dedicated to the memory of Professor Iwao Tabushi.

(2) On leave from Chung-Ang University, Seoul, Korea.

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(13) **5**: ^1H NMR ($CDCl_3$) 8.18 (2 H, br s, isophth CONH), 8.09 (3 H, m, pyr-3H, isophth-2H), 7.92 (6 H, m, pyr-5H, CH_2CONH, isophth-4, 6H), 7.76 (2 H, t, J = 8 Hz, pyr-4H), 7.64 (1 H, br t, isophth-5H), 7.02 (4 H, d, J = 9 Hz, phenol-3,5H), 6.71 (4 H, d, J = 9 Hz, phenol-2,6H), 4.03 (4 H, t, J = 5.5 Hz, CH_2O), 2.57 (4 H, m, CH_2CO), 2.19 (4 H, m, CH_2CH_2O), 1.54 (6H, s, CH_3); mass spectrum M^+ 712.3028 $C_{41}H_{40}N_6O_6$ requires 712.3009.

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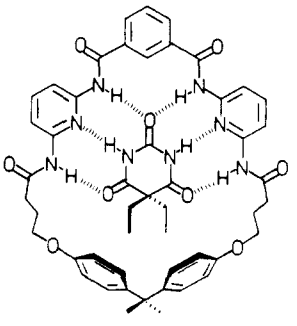
Table I. Association Constants for the Receptor-Barbiturate Interaction[a]

receptor	barbiturate	K_a, M^{-1} (25 °C, $CDCl_3$)
6	barbital (**1b**)	2.08×10^4
5	mephobarbital (**1d**)	6.80×10^2
5	phenobarbital (**1c**)	1.97×10^5
5	barbital (**1b**)	1.37×10^6

[a] At 250 MHz: [receptor] = 2.0×10^{-3} M, [barbiturate] = 4.0×10^{-2} M. Measurements made on isophthaloyl-2H and both amide-NHs by using 12-15 points. In all cases titration curves showed distinct 1:1 stoichiometry.

the hexa-hydrogen-bonded complex **7**.[14] The CH_2 and CH_3 resonances of the barbital ethyl groups were shifted upfield by 0.25 and 0.23 ppm, respectively, confirming their proximity to the diphenylmethane cleft in **7**. Furthermore, the isophthaloyl resonances in uncomplexed **5** are broadened due to the conformational mobility of the macrocycle. In complex **7** the motion of the isophthaloyl group is restricted and its ^1H resonances sharpen. CPK molecular modeling suggests that in **7** the isophthaloyl-2 proton is forced to lie in the deshielding region of the barbital-2-carbonyl group, and, indeed, this resonance is shifted downfield by 0.4 ppm.



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Association constants for the receptor-barbiturate complexes were determined from ^1H NMR titration data by using either Foster-Fife[15] or nonlinear least-squares analysis and are collected in Table I. The three key design features of the receptors (their macrocyclic structure, the six H-bonding interactions, and the 5,5-binding region) are confirmed by these measurements. Good complementarity between barbiturate **1b** and macrocyclic receptor **5** results in a large association constant (1.37×10^6 M^{-1}). When the inwardly pointing binding site is no longer enforced, with acyclic **6**, association to **1b** diminishes by almost 100-fold. Removal of three H-bonds from the binding interaction, as with mephobarbital **1d**, leads to a more than 1000-fold decrease in binding to **5**. Incorporation into the barbiturate-5 position of a bulky substituent which cannot fit neatly into the receptor cavity, e.g., with phenobarbital **1c** and **5**, causes a 10-fold reduction in the binding constant.

In summary, we have shown that complementary positioning of H-bonding groups within a cavity can lead to strong complexation between uncharged molecules. We are currently seeking to increase the recognition characteristics of these receptors, particularly in the 5,5-region, and to extend the approach to other key biological molecules such as urea, uric acid, and xanthine.

Acknowledgment. We thank KOSEF, Korea for a fellowship to S.K.C. and the National Institutes of Health for financial support of this work.

(14) Complex (1:1) between **1b** and **5**: ^1H NMR ($CDCl_3$) 12.40 (2 H, s, barb NH), 9.80 (2 H, s, isophth CONH), 9.55 (2 H, s, CH_2 CONH), 8.49 (1 H, s, isophth-2H), 8.20 (2 H, d, J = 8 Hz, pyr-3H), 8.15 (2 H, d, J = 8 Hz, pyr-5H), 7.98 (2 H, d, J = 8 Hz, isophth-4H), 7.84 (2 H, t, J = 8 Hz, pyr-4H), 7.64 (1 H, t, J = 8 Hz, isophth-5H), 7.04 (4 H, d, J = 9 Hz, phenol-3,5H), 6.73 (4 H, d, J = 9 Hz, phenol-2,6H), 4.06 (4 H, t, J = 5.5 Hz, CH_2O), 2.66 (4 H, t, J = 7 Hz, CH_2CO), 2.15 (4 H, m, CH_2CH_2O), 1.78 (4 H, q, J = 7.5 Hz, CH_3CH_2), 1.65 (6 H, s, CH_3), 0.65 (6 H, t, J = 7.5 Hz, CH_3CH_2).

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Lewis Acid Promoted Carbon-Carbon Bond Formation between Bridging Isocyanides

Jianxin Wu, Phillip E. Fanwick,† and Clifford P. Kubiak*[1]

Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Received November 2, 1987

We report the direct formation of a carbon-carbon bond between two aryl isocyanides of a binuclear iridium(0) complex by using a Lewis acid promoter. Carbon-carbon bond-forming reactions are among the most important organic chemical transformations mediated by transition-metal complexes. There has been a particularly keen interest recently in coupling pairs of coordinated carbonyl[2-4] or isocyanide[5] ligands of mononuclear[3,5] and binuclear[2,4] transition-metal complexes. The coupling of the isocyanide ligands of the complex $Ir_2(CNR)_4(dmpm)_2$[8,9] (**1**, R = 2,6-$Me_2C_6H_3$, dmpm = $Me_2PCH_2PMe_2$), described herein, is unusual in several respects. Coupling is mediated by a late transition-metal complex, a d^9-d^9 Ir(0) system. The reaction does not require two external reducing electronic equivalents. Instead, coupling is effected by formal addition of a single $^{\bullet}AlEt_2$ radical to two μ-isocyanides resulting in annulation to a five-membered C_2N_2Al ring.

In view of the theoretical criteria for isocyanide coupling enumerated recently,[6] complex **1** appears to be extremely promising. The complex possesses the "cradle" type[10] structure I[9,11,13-15]

† Address correspondence pertaining to crystallographic studies to this author.

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(8) Complex **1** was prepared by Na/Hg reduction of $[Ir_2(2,6\text{-}Me_2C_6H_3CN)_5(dmpm)_2][PF_6]_2$[7] in benzene. Anal. Calcd for $C_{48}H_{66}N_4P_4Ir_2$ ($\mathbf{1}\cdot{}^1/_3C_6H_6$): C, 47.75; H, 5.51; N, 4.64. Found: C, 47.55; H, 5.72; N, 4.43. (A solvated benzene molecule is confirmed by the X-ray structural study and is partially removable under high vacuum.) Spectroscopic data: IR (KBr) ν(CN) 2038 (s), 1996 (s, br), 1600 (m), 1564 (m) cm^{-1}; ^{31}P NMR (81 MHz, benzene, reference to external H_3PO_4) δ -34.7 (s, br); ^1H NMR (200 MHz, toluene-d_8) δ 6.9 (m, 12 H, $C_6H_3(CH_3)_2$), 2.51 (s, 12 H, $C_6H_3(CH_3)_2$), 2.37 (s, 12 H, $C_6H_3(CH_3)_2$), 1.70 (s, 12 H, PCH_3), 1.08 (s, 12 H, PCH_3), 0.89 (m, 4 H, PCH_2P).

(9) Crystal data for $\mathbf{1}\cdot C_6H_6$: $C_{52}H_{70}N_4P_4Ir_2$, fw = 1259.5, monoclinic, space group $P2_1$, a = 10.615 (2) Å, b = 16.883 (3) Å, c = 15.044 (3) Å, β = 94.23 (1)°, V = 2689 (2) Å^3, Z = 2, d_{calcd} = 1.555 g cm^{-3}. The structure was solved by MULTAN least-squares Fourier methods and was refined to R and R_w values of 0.033 and 0.044, respectively, for 528 variables and 3229 unique observations with $I > 3\sigma(I)$ with Mo Kα radiation. Data were corrected for absorption empirically. Changing the enantiomer did not significantly change the R factors.

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