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Received: April 16, 2002
Revised: June 17, 2002 [Z19098]

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Guest Preorganization: An Alternative "Bioinspired" Paradigm in Host–Guest Chemistry**

Brian S. Hammes, Xuemei Luo, Mary W. Carrano, and Carl J. Carrano*

The tris(pyrazolyl)borate ligands pioneered by Trofimenko in the late 1960s, have arguably become the preeminent platform for metal binding in coordination, organometallic, and bioinorganic chemistries.[1] Indeed, complexes of this ligand with almost every metal in the periodic table are known.[1] Modifications to the parent ligand over the last few decades have been primarily directed towards the synthesis of highly sterically congested analogues that have allowed the stabilization of species not previously accessible.[2–5] Another possible application for this anionic, three-fold-symmetric class of molecule, namely as a "host" to something other than a metal ion, seems to have been largely unexplored. Recently, by using ester- or amide-containing R groups at the 3-position of the pyrazole ring to provide an additional set of sites for secondary interactions, we have begun to explore the host–guest chemistry of the tris(pyrazolyl)borates. Whilst trying to use various transamidation reactions to convert 3-ester-substituted Tp (tris(pyrazolyl)borates) ligands into 3-amido-substituted ligands we isolated complexes of the general stoichiometry $[Tp^*][NH_3R]$, where Tp^* = tris(3-carboxyethyl-5-methylpyrazolyl)borate. That these species were not simple salts but true host–guest complexes was revealed by an X-ray crystal structure of the *tert*-butylammonium analogue, **1**.[6] The structure of **1** (Figure 1) reveals the expected complementarity of fit between the anionic tris(pyrazolyl)borate and the cationic three-fold symmetric protonated amine which is lodged in the "metal-binding" cavity of the former. In addition to the electrostatic attraction, the protonated amine group makes three strong, bifurcated hydrogen bonds with the pyrazole nitrogen atoms and the ester carbonyl groups. The hydrogen atoms of the ammonium ion, which were all easily located and refined in the structure, are at an average of 2.16(6) Å from the pyrazole nitrogen atoms and 2.54(16) Å from the carbonyl oxygen atoms, with 71.6(26)° N–H···O angles. Two sharp N–H proton resonances

[*] Dr. C. J. Carrano, Dr. X. Luo, M. W. Carrano
Department of Chemistry and Biochemistry
Southwest Texas State University
San Marcos, TX 78666 (USA)
Fax: (+1) 512-245-2374
E-mail: cc05@swt.edu
Dr. B. S. Hammes
Department of Chemistry
St. Joseph's University
Philadelphia, PA (USA)

[**] This work was supported in part by Grants AI-1157 from the Robert A. Welch Foundation and CHE-9726488 from the NSF. The NSF-ILI program grant USE-9151286 is acknowledged for partial support of the X-ray diffraction facilities at Southwest Texas State University. We also thank Prof. Michael Blanda for valuable discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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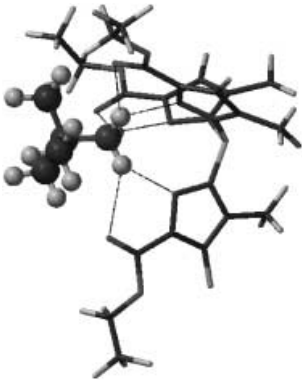

Figure 1. The structure of $[(CH_3)_3CNH_3][Tp^{CO_2Et,Me}]$ (**1**). The host $Tp^{CO_2Et,Me}$ is depicted as a tube model while the guest $(CH_3)_3CNH_3$ is shown as a ball-and-stick structure. Dotted lines indicate the bifurcated hydrogen bonds.

corresponding to free and bound alkyl ammonium ion in slow exchange are observable by NMR spectroscopy in $CDCl_3$ for methylamine, while a single broad resonance, indicative of intermediate exchange, is seen with *tert*-butylamine, which reveals that there is thermodynamic and/or kinetic discrimination between amines.

While this type of host–guest interaction promises to provide possible applications for Tp-based hosts in the sensing of, for example, amino acids and neurotransmitters, it is not in any way unique in supramolecular chemistry. It follows the accepted paradigm in that the host is preorganized to accept a particular guest based on size, shape, and electrostatic complementarity.[7] However, this paradigm requires that a new host be designed and synthesized for each guest or at least each class of guest. Nature often takes a different approach to the question of recognition. For example, iron uptake in microbes is a receptor-mediated event but the metal cation is first attached to a siderophore molecule which serves not only to solubilize the iron but also to provide the recognition sites.[8] These recognition sites arise because the siderophore adopts a specific 3D structure, based on the coordination preferences of the iron center (in some cases the siderophore itself may also preorganized to provide high thermodynamic stability). In general, neither the metal ion nor the siderophore itself are recognized, but only the complex of the two. In this way, a single receptor is able to recognize iron complexes based on a variety of siderophores; possibly a competitive advantage to some organisms. That, in this case, the desired guest is the metal ion rather than the ligand does not detract from the basic concept. Another relevant example concerns the so-called zinc fingers. These are small metal-binding peptide units that function in gene regulation by promoting protein–nucleic acid binding and recognition.[9] All these proteins contain a core of histidine and cysteine residues which, when coordinated to a zinc center in a tetrahedral fashion, are stabilized in variety of folding motifs critical to DNA recognition. In this case, the protein ligands themselves have no DNA-binding specificity in the absence of the metal ion. It is only after they are "preorganized" by metal coordination that interaction is observed. To illustrate the utility of this approach, we have taken the guest molecule 3-methylcarboxamido-5-methylpyrazole, which has no affinity for the Tp* host, and preorganized it for recognition by taking advantage of the coordination preferences of Ni^{II} centers. Thus, reaction of Ni^{II} with three equivalents of the pyrazole produces the dicationic tris octahedral complex, in which the pyrazole functions as a bidentate ligand, coordinating through a pyrazole nitrogen atom and the amide carbonyl group. In this way, the remaining three uncoordinated pyrazole nitrogen atoms have their protons arranged in a trigonal array that is highly complementary to the pyrazole nitrogen atoms of the Tp* "host". An X-ray structure of **2** (Figure 2) reveals a host–guest complex stabilized by both electrostatic interactions and hydrogen

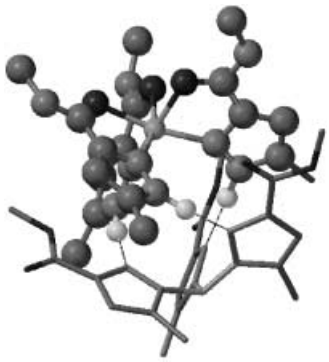

Figure 2. The structure of the cationic portion of $[Ni(pz^{CONHMe,Me})_3][Tp^{CO_2Me,Me}]ClO_4$ (**2**). The host $Tp^{CO_2Me,Me}$ is depicted as a tube model while the guest $[Ni(pz^{CONHMe,Me})_3]^{2+}$ shown as a ball-and-stick structure. All hydrogen atoms, except those involved in H-bonding (dotted lines), have been removed for clarity.

bonding, with an average N···N distance of 2.87(3) Å and a N_{pz}–H···N_{Tp} angle of 172(1).[10] The perchlorate counterion needed for the charge balance of the $\{[Ni(pz^{CONHMe,Me})_3][Tp^{CO_2Me,Me}]\}^+$ complex unit does not interact.

In conclusion, we have shown for the first time that an elaborated version of the widely utilized tris(pyrazolyl)borate class of ligand can function as a host for something other than a metal cation. In addition, we show an example of an alternate paradigm in host–guest chemistry in which a simple pyrazole guest with no inherent affinity is preorganized, by coordination to a metal ion, to bind to a Tp host.

Experimental Section

Complex **1** was isolated during the attempted aminolysis of potassium tris(3-carboxyethyl-5-methylpyrazolyl)borate (5.1 g, 0.1 mol) with $Al(CH_3)_2NH^tBu$ in refluxing dichloromethane. Acidic workup, extraction, and recrystallization from diethyl ether gave large crystals of **1** (1.0 g) suitable for crystallographic analysis. Elemental analysis (%) calcd for $[(CH_3)_3CNH_3][Tp^{CO_2Et,Me}]$, $C_{25}H_{40}N_7O_6B{\cdot}0.5\,H_20$: C 54.59, H 7.44, N 17.83; found C 54.51, H 7.39, N 17.84; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 8.10$ (br s, 3H; N*H*$_3$), 6.37 (s, 3H; Pz*H*), 4.28 (q, $J = 7$ Hz, 6H; -OC*H*$_2$-), 2.32 (s, 9H; Pz-C*H*$_3$), 1.54 (s, 9H; *tert*-butyl-C*H*$_3$), 1.31 ppm (t, $J = 7$ Hz, 9H; -CH$_2$-C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): $\delta = 164.30$, 144.70, 142.89, 106.92, 60.12, 51.31, 27.02, 14.41, 12.79 ppm; FTIR (KBr): $\tilde{\nu} = 2497$ (B-H), 1714 cm^{-1} (C=O). Pz = pyrazolyl.

Compound **2** was prepared by a one-pot reaction by adding 3-methylcarboxamido-5-methylpyrazole (0.204 g, 1.5 mmol) to the complex $[Tp^{CO_2Et,Me}Ni(H_2O)_3]ClO_4$[11] (0.31 g, 0.5 mmol) in methanol, followed by overnight stirring. After evaporation of the solvent under reduced pressure, the light-blue solid was dissolved in acetonitrile. Slow diffusion of diethyl ether into a concentrated acetonitrile solution produced crystals suitable for X-ray diffraction. Caution! The perchlorate salt is potentially explosive and should be handled with care. Elemental analysis (%) calcd for $[(pz^{CONHMe,Me})_3Ni][Tp^{CO_2Me,Me})]ClO_4{\cdot}ACN{\cdot}3\,H_2O$, $C_{38}H_{57}N_{16}O_{16}BClNi$: C

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41.55, H 5.23, N 20.42; found C 41.31, H 4.70, N 20.34; FTIR (KBr): $\tilde{\nu}$ = 2564 (B-H), 1722, 1634 cm^{-1} (C=O); $\lambda_{max}(CH_3CN, \varepsilon, M^{-1}cm^{-1})$: 378 (20).

Received: May 14, 2002 [Z19292]

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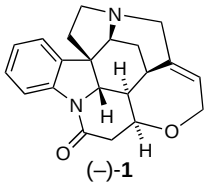
A Concise Formal Total Synthesis of (±)-Strychnine by Using a Transannular Inverse-Electron-Demand Diels–Alder Reaction of a [3](1,3)Indolo[3](3,6)pyridazinophane**

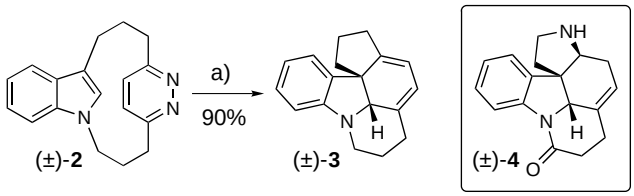
Graham J. Bodwell* and Jiang Li

Owing to its level of complexity for its size, strychnine (**1**) presents a most formidable synthetic challenge.[1] The first total synthesis, one of the most significant achievements in the history of organic synthesis, was reported by Woodward[2] in 1954 and it wasn't until the early 1990s that a series of other successful syntheses, both racemic and enantioselective, began to appear. There are now ten reported total syntheses of strychnine[2–11] and each of them features an elegant application of one or more reactions that bring about a substantial increase in molecular complexity, for example, the Mannich reaction combined with a sigmatropic rearrangement (Overman and co-workers,[3] Kuehne et al.[4,5]), the intramolecular Diels–Alder reaction (Rawal et al.,[6] Martin and co-workers[7]), intramolecular Heck reactions (Rawal et al.,[6] Bonjoch, Bosch, and co-workers[8]), the cobalt-mediated [2+2+2] cycloaddition (Vollhardt and co-workers[9]), skeletal rearrangements (Stork,[10] and Martin and co-workers[7]) and transannular oxidative cyclization (Magnus et al.[11]). The shortest synthesis reported to date is that of Vollhardt (14 steps from propiolic acid), but the highest overall yield (10%) belongs to Rawal's synthesis.[6,12]



(–)-**1**

We recently reported the synthesis of cyclophane (±)-**2** and its efficient transannular inverse-electron-demand Diels–Alder (IEDDA) reaction to afford pentacycle (±)-**3** (Scheme 1).[13] The similarity of (±)-**3** to the key pentacyclic amine (±)-**4** (ABCEG rings of strychnine) described by Rawal[6] prompted us to attempt to apply our "cyclophane approach" to a formal total synthesis of (±)-strychnine.



(±)-**2** (±)-**3** (±)-**4**

Scheme 1. Conversion of (±)-**2** into (±)-**3**. Reagents and conditions: a) *N*,*N*-diethylaniline, Δ, 48 h.

The synthesis (Scheme 2) commenced with the reaction of the tryptamine **5** with 3,6-diiodopyridazine[14] to afford iodide **6** (100%). N-Allylation of the indole moiety yielded **7** (91%), which was subjected to a sequential hydroboration/intramolecular B-alkyl Suzuki-Miyaura cross-coupling reaction[15] to give cyclophane (±)-**8** (65%). The secondary amine was protected as a methyl carbamate and the resulting cyclophane (±)-**9** (96%) was heated in *N*,*N*-diethylaniline to induce the key transannular IEDDA reaction. Pentacycle (±)-**10**, the product of the transannular IEDDA reaction followed by the expulsion of N_2 from the initially formed adduct,[13] was obtained quantitatively. This very productive step resulted in the generation of two stereogenic centers (including the key quaternary center[1b]) with the correct relative stereochemistry[13] and the simultaneous construction of the C, E, and G rings.

Having rapidly constructed the ABCEG framework, a short series of functional group interconversions were required to prepare (±)-**4**. Reduction of (±)-**10** with $NaBH_4$/CF_3CO_2H occurred with complete chemo- and stereoselectivity to afford (±)-**11** (100%). The tertiary amine was then oxidized with PDC[16] to give the amide (±)-**12** (30%) and removal of the carbamate protecting group delivered Rawal's

[*] Dr. G. J. Bodwell, J. Li
Department of Chemistry
Memorial University of Newfoundland
St. John's, NF, A1B 3X7 (Canada)
Fax: (+1) 709-737-3702
E-mail: gbodwell@mun.ca

[**] Support of this work from the Natural Sciences and Engineering Research Council (NSERC) of Canada is gratefully acknowledged.

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