Scheme I. Solid-Phase Assembly of an N-Substituted Glycine from Two Submonomers

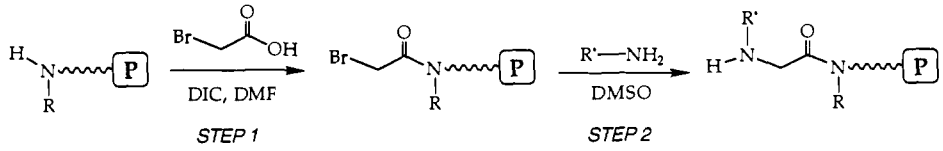
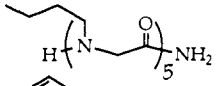
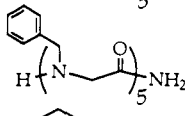
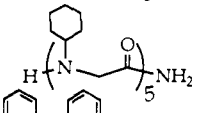
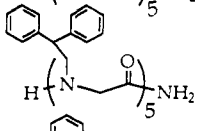
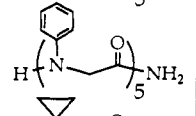
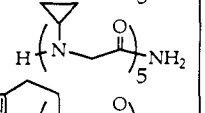
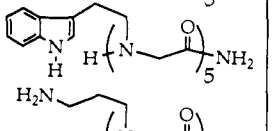
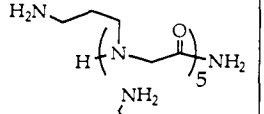
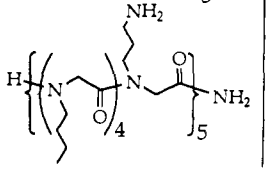


Table I. Oligo(N-Substituted Glycines) Prepared by the Submonomer Method

Oligomer	Crude product characteristics		
	purity (%) [a]	yield (%) [b]	mass (MH^+) [c]
	>85	90	583.5
	>85	74	753.2
	>85	79	713.4
	>85	70	1204.1
	>85	83	683.3
	>85	83	503.3
	>60	52	1018.4
	>85	63 [d]	588.4
	>65	86 [d]	2850.9

[a] Determined by HPLC. [b] Determined from dry weight. [c] Liquid-matrix secondary-ion mass spectrometry. [d] Made from Boc-NH-$(CH_2)_3NH_2$.

Using optimized synthetic conditions[2] eight penta(NSGs) were prepared by the submonomer method from a variety of amines, including poorly nucleophilic, sterically-hindered, and side-chain-protected amines. The purity, yields, and mass spectrometry data on the pentamers are shown in Table I. All compounds were successfully synthesized as established by mass spectrometry, with isolated crude yields between 52 and 90% and purities generally greater than 85% by HPLC.[5]

A 25-mer, $[(N\text{-butylglycine})_4(N\text{-(3-aminopropyl)glycine})]_5$, was synthesized by the submonomer method, thereby demonstrating the utility of this method for the preparation of longer oligomers. Mass spectroscopy confirmed the identity of this compound (MH^+ = 2850.9), which was obtained in 86% yield and 65% purity by HPLC.[5]

The efficient synthesis of a wide variety of oligomeric NSGs using robotic synthesis technology, as presented here, makes these polymers attractive candidates for the generation and rapid screening of diverse peptidomimetic libraries. The compatibility of this method with conventional peptide synthesis should allow the incorporation of novel structures into peptides. Furthermore, the solid-phase submonomer method should allow the efficient synthesis of a wide variety of novel N-substituted biopolymers.

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Bioorganometallic Chemistry. 1. Synthetic and Structural Studies in the Reactions of a Nucleobase and Several Nucleosides with a (η^5-Pentamethylcyclopentadienyl)rhodium Aqua Complex

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Interactions of metal complexes with DNA/RNA nucleobases, nucleosides, nucleotides, and oligonucleotides have been extensively studied in order to determine the mode of action of these metal complexes as a consequence of drug activity, as useful tools for molecular biology, and as regulators of gene expression.[1] The great majority of these bonding studies have been carried out with inorganic complexes,[2] while few have utilized organometallic compounds.[3]

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[†] Lawrence Berkeley Laboratory.
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(1) (a) Tullius, T. D. In *Metal-DNA Chemistry*; Tullius, T. D., Ed.; ACS Symposium Series 402; American Chemical Society: Washington, D. C., 1989; Chapter 1 and references therein. (b) Barton, J. K. *Comments Inorg. Chem.* **1985**, *3*, 321 and references therein. (c) Pyle, A. M.; Barton, J. K. In *Progress in Inorganic Chemistry, Bioinorganic Chemistry*; Lippard, S. J., Ed.; J. Wiley and Sons: New York, 1990; Vol. 38, p 413 and references therein.

(2) (a) Marzilli, L. G. In *Progress in Inorganic Chemistry*; Lippard, S. J., Ed.; J. Wiley and Sons: New York, 1977; Vol. 23, p 255 and references therein. (b) Howe-Grant, M. E.; Lippard, S. J. *Met. Ions Biol. Syst.* **1980**, *11*, 63 and references therein. (b) Raudaschl-Sieber, G.; Schollhorn, H.; Thewalt, U.; Lippert, B. *J. Am. Chem. Soc.* **1985**, *107*, 3591. (c) Reily, M. D.; Hambley, T. W.; Marzilli, L. G. *J. Am. Chem. Soc.* **1988**, *110*, 2999. (d) Alink, M. A.; Nakahara, H.; Hirano, T.; Inagaki, K.; Hakanishi, M.; Kidani, Y.; Reedijk, J. *Inorg. Chem.* **1991**, *30*, 1236 and references therein. (e) Reily, M. D.; Marzilli, L. G. *J. Am. Chem. Soc.* **1986**, *108*, 8299. (f) Qu, Y.; Farrell, N. *J. Am. Chem. Soc.* **1991**, *113*, 4851 and references therein. (g) Caradonna, J. P.; Lippard, S. J.; Gait, M. J.; Singh, M. *J. Am. Chem. Soc.* **1982**, *104*, 5793. (h) Marcelis, A. T. M.; den Hartog, J. H. J.; Reedijk, J. *J. Am. Chem. Soc.* **1982**, *104*, 2664. (i) Sherman, S. E.; Gibson, D.; Wang, A. H.-J.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 7368. (j) Mukundan, S., Jr.; Xu, Y.; Zon, G.; Marzilli, L. G. *J. Am. Chem. Soc.* **1991**, *113*, 3021. (l) Pneumatikakis, G.; Hadjiliadis, H. *J. Chem. Soc., Dalton Trans.* **1979**, 596. (m) Rainen, L.; Howard, R. A.; Kimball, A. P.; Bear, J. L. *Inorg. Chem.* **1975**, *14*, 2752. (n) Torres, L. M.; Marzilli, L. G. *J. Am. Chem. Soc.* **1991**, *113*, 4678. (o) Scheller, K. H.; Mitchell, P. R.; Prijs, B.; Sigel, H. *J. Am. Chem. Soc.* **1981**, *103*, 247. (p) Sigel, H. In *Metal-DNA Chemistry*; Tullius, T. D., Ed.; ACS Symposium Series 402; American Chemical Society: Washington, D. C., 1989; Chapter 11 and references therein. (q) Hodgson, D. J. In *Progress in Inorganic Chemistry*; Lippard, S. J., Ed.; J. Wiley and Sons: New York, 1977; Vol. 23, p 211.

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Table I. ^{1}H NMR (500 MHz) Data for 9-MA, Ado, Guo, and Cp*Rh Complexes **2**–**4** in DMSO-d_6[a]

nucleobase/ Cp*Rh complex	H2[b]	H8	NH6	NH1/NH$_2$2	Cp*
9-MA	8.14 (1)	8.08 (1)	7.17 (2)		
2	7.67 (1)	8.83 (1)	4.51 (1)		1.80 (15)
Ado	8.11 (1)	8.33 (1)	7.33 (2)		
3	7.62 (1)	8.92 (1)	4.59 (1)		1.80 (15)
Guo		7.92 (1)		10.62(1)/6.44(2)	
4		8.94 (1)		11.5(1)/6.92(2)	1.71 (15)

[a] Proton chemical shifts relative to TMS. [b] Number in parentheses denotes the number of protons from integration.

In recent years, we have investigated the coordination chemistry of the highly electrophilic (η^5-pentamethylcyclopentadienyl)rhodium dicationic complex, $[Cp^*Rh(S)_3]^{2+}$ (S = CH_3COCH_3 or CH_3CN), with nitrogen heterocyclic compounds.[4] The potential of a similar water-soluble complex or a derivative[5] being able to coordinate to the nitrogen atoms of biological ligands and, perhaps, be a useful reagent for sequencing and mapping DNA bases in conjunction with surface microscopy techniques for application to the human genome[6] as well as a possible antitumor agent[7] led us to initiate bonding studies in this fascinating area of bioorganometallic chemistry. In this communication, we will focus on a water-soluble (η^5-pentamethylcyclopentadienyl)rhodium aqua complex, **1**, and describe the various bonding modes of complex **1** with a nucleobase and several nucleosides in aqueous and dimethyl sulfoxide (DMSO) solutions.

Reaction of $[Cp^*Rh(OTf)_2]_x$ (OTf = $CF_3SO_3^-$, supplementary material) with deoxygenated water provides, after lyophilization, a yellow solid, **1**. The elemental analysis gave an empirical formula for **1** of $[Cp^*Rh(H_2O)_2(OTf)_2]_x$, while the FAB-MS data of **1** were consistent with a dimeric species (glycerol/H_2O; m/z = 688.9, $[Cp^*Rh(OH)]_2(OTf) - 4H)$.[8] The two p$K_a$'s for **1** were determined titrimetrically to be 2.8 and 5.3, and thus, we believe that complex **1** is a Cp*Rh–μ–hydroxy dimer species at pH 5–7 where we conducted our synthesis and NMR experiments with the nucleobase and the nucleosides.

Complex **1** was reacted with 9-methyladenine (9-MA) in D_2O at pD 7.2 (pD = pH + 0.4) to provide evidence, by ^{1}H NMR spectroscopy, for the formation of a Cp*Rh–9-MA complex, **2**, with dramatic chemical shifts for both H2 and H8, in comparison to free 9-MA, at 8.51 and 7.62 ppm. By utilizing 9-MA-d[9] that is selectively deuterated at H8, we were able to unequivocally assign the chemical shifts to each proton of **2** and show that H8 was shifted 0.75 ppm downfield from free 9-MA, while H2 was shifted 0.47 ppm upfield in DMSO-d_6 (Table I)! It is interesting to note that formation of complex **2** occurs over the pD range of 6–9 and that it is stable for over 1 week at ambient temperature (NMR, pD 7.2).

Complex **2** was isolated and purified by recrystallization from methanol to yield an orange solid (26%) that was found by FAB-MS (m/z = 1456.7, M – OTf), single-crystal X-ray crystallography, and elemental analysis to have the unusual and unprecedented structure of a cyclic trimer (Figure 1).[10] Previously

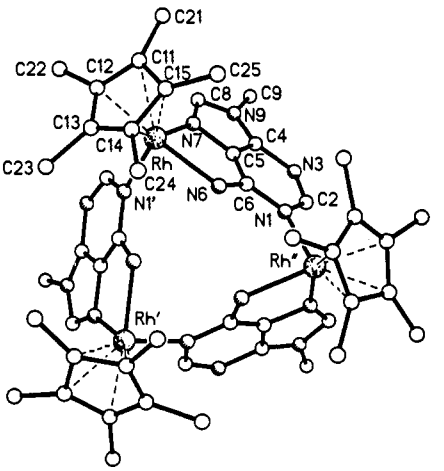

Figure 1. Computer-generated diagram of complex **2**, $[Cp^*Rh(9\text{-methyladenyl})]_3(O_3SCF_3)_3\cdot 6H_2O$. Selected bond lengths (Å) and angles (deg): Rh–N6, 2.181 (16); Rh–N7, 2.08 (2); Rh–N1′, 2.10 (2); Rh–C15, 2.22 (3); N6–Rh–N7, 79.5 (7); N6–Rh–N1′, 88.7 (8); N7–Rh–N1′, 84.2 (9); Rh–N6–C6, 113.4 (13); Rh–N7–C5, 108.3 (15); C6–C5–N7, 122 (2); C5–C6–N6, 117 (2); N7–Rh–C15, 119.8 (10). The dihedral angle between the two 9-MA planes is 82.3°.

reported studies have verified an N6–N7, 5-membered-ring chelate of 9-MA with a Cp_2Mo center[3] and a μ-N1 and N7 bridging of 9-MA between metal centers (e.g., Rh^{2+}, Ag^+, Co^{2+}),[11,12] but no metal–9-MA complex has been reported as yet incorporating both bonding features in one molecule, as is shown in **2**. Clearly, the formation of the 12-membered-ring cyclic trimer results from the ability of the Cp*Rh cation to act as an azaphile with the favorable geometry of N1 poised to form the third bond to a Cp*Rh of an adjacent $[Cp^*Rh(\eta^2(N6,N7)\text{-9-methyladenyl})](OTf)$ moiety.

Reaction of **1** with adenosine (Ado) in H_2O at pH 7.1 also provided a complex, which was isolated[13] and analyzed by ^{1}H NMR (DMSO-d_6) spectroscopy to give chemical shifts for H8 (8.92 ppm) and H2 (7.62) similar to those observed for complex **2** and, thus, we conclude that Ado also forms a cyclic trimer, **3** (Table I). In contrast, it was found that guanosine (Guo) reacted with **1** at pH 5.4 to provide an isolated complex that by elemental analysis and FAB-MS (m/z = 670.1, [Cp*Rh(Guo)(OTf)]) was a monomer with the formula $[Cp^*Rh(Guo)(H_2O)(OH)](OTf)$ (**4**).[14] The structure of **4** was elucidated by ^{1}H NMR spectroscopy in DMSO-d_6 to show a substantial downfield shift for H8 at 8.93 ppm (Δ = 1.02 ppm), which is entirely consistent with exclusive N7 binding to the Guo nucleus.[1b,2i,q] The bonding differences between Ado and Guo for **1** reflect the geometry of the N7 and exocyclic NH_2 positions for 5-membered-ring chelate formation via a condensation reaction of the exocyclic NH_2 group with a reactive Cp*Rh hydroxy species, as well as the disposition of the N1 position in the Ado nucleus versus the lack of comparable

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(7) Lippert, B. In *Progress in Inorganic Chemistry*; Lippard, S. J., Ed.; J. Wiley and Sons: New York, 1989; Vol. 37, p 1.

(8) Complex **1**, $[Cp^*Rh(H_2O)_2(OTF)_2]_x$, Anal. Calcd for $RhO_8S_2F_6C_{12}H_{19}$: C, 25.18; H, 3.35. Found: C, 25.01; H, 3.30.

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(10) Complex **2**, $[Cp^*Rh(9\text{-MA})]_3(O_3SCF_3)_3\cdot 6H_2O$, Anal. Calcd for $Rh_3O_{15}S_3F_9N_{15}C_{51}H_{75}$: C, 35.74; H, 4.41; N, 12.26. Found: C, 35.44; H, 3.57; N, 11.38. Crystals of **2** were obtained from methanol at –30 °C; space group $R3c$; a = 22.762 (5) Å, c = 24.341 (9) Å; V = 10921 (6) Å^3; Z = 6, T = 130 K. The structure was solved by direct methods and was refined (4671 reflections) to the final values of the residuals R = 0.106 and R_w = 0.114. Diffraction data was collected on a Syntex P2$_1$ diffractometer. The structure-solving program used was the Siemens SHELXTL PLUS (VMS).

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(13) Due to the difficulties in removing small amounts of free adenosine in the recrystallization of complex **3** we could not get a satisfactory elemental analysis, but the NMR data is conclusive for the structure assigned.

(14) Complex **4**, $[Cp^*Rh(guanosine)(OH)(H_2O)](O_3SCF_3)$, Anal. Calcd for $RhO_{13}S_1F_3N_5C_{21}H_{32}$: C, 33.43; H, 4.27; S, 4.25; N, 9.28. Found: C, 33.40; H, 4.10; S, 3.86; N, 9.17.

bonding sites in the Guo nucleus.

Future bonding studies with complex **1** will be concerned with nucleobases, nucleotides, and oligonucleotides and the role of steric effects in the ability of Cp*Rh to form terminal or intrastrand bonds with adenine or guanine oligomers.[2i,7] As well, the use of the Cp*Rh aqua complex, **1**, as an anchor for DNA molecules to various microscopy surfaces[15] and its biological activity[16] will also be reported in future publications.

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Supplementary Material Available: Listings of spectroscopic data and synthetic procedures for complexes **1-4** and $[Cp^*Rh(OTf)_2]_x$ and tables of crystal data, atomic coordinates, isotropic displacement coefficients, bond lengths, bond angles, and anisotropic displacement coefficients (9 pages); table of observed and calculated structure factors for **2** (8 pages). Ordering information is given on any current masthead page.

(15) Zuccheri, G.; Smith, D. P.; Fish, R. H.; Maestre, M. F. Manuscript in preparation.
(16) Gold-Goldstein, R.; Tischler, A.; Fish, R. H. Manuscript in preparation.

Preference of *cis*-Amide Structure in *N*-Acyl-*N*-methylanilines

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The amide bond in *N*-methylbenzanilide (**1**, Chart I) is cis in the crystal and in solution, whereas that of benzanilide itself is trans.[1,2] The *cis*-amide preference in *N*-methylamides with two aromatic groups is general.[3,4]

The structures of four *N*-acyl-*N*-methylanilides with a nonaromatic group at the carbonyl end, i.e., isopropenyl (**2**), cyclopropyl (**3**), isopropyl (**4**), and *tert*-butyl (**5**), were examined by X-ray crystal analyses. It was proved that the molecules of all these compounds adopt the *cis*-amide structure in the crystal. The amide bonds were almost planar with torsion angles (C—N—C(=O)—C) of 5.0°, -1.2°, -1.4°, and 5.0° for **2**, **3**, **4**, and **5**, respectively, as were observed in ordinary amide compounds.[5] Overall molecular structures of these compounds, together with that of **1**, are illustrated by ORTEP drawings in Figure 1.

There were no significant differences in bond lengths and angles related to the amide bond among the four compounds **2-5**. The mean value of the amide C—N bond length was 1.354 Å, which is intermediate between the single-bond C—N length of 1.47 Å and the double-bond C=N length of 1.24 Å.[6] The summations of the three valence angles around the nitrogen were almost 360°,

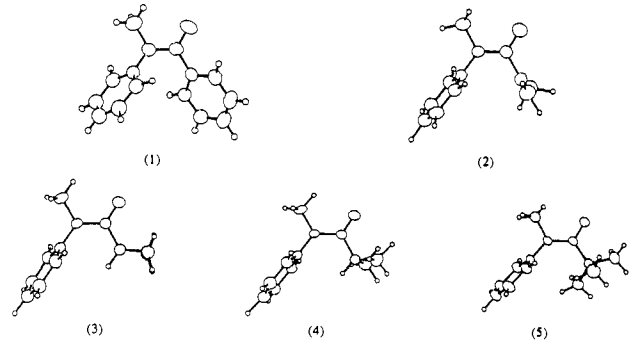
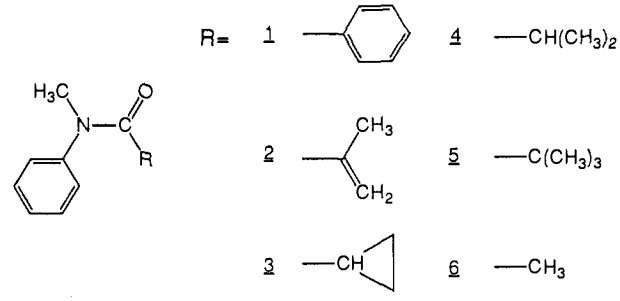


Figure 1. The ORTEP drawings of the molecules **1-5**.

Chart I



indicating the sp^2 character of the nitrogen atom. These facts suggest that the *N*-methyl amide bond in cis conformation retains partial double bond character similar to that of a free amide bond in trans conformation (1.34 Å in proteins and peptides and 1.376 Å in gaseous formamide[6]), and the hybridization nature of the amide nitrogen atom is not affected by N-methylation. On the other hand, interplanar angles between the phenyl ring and amide group were 60.0° for **1**, 96.9° for **2**, 84.2° for **3**, 78.2° for **4**, and 81.6° for **5**. The values indicate that the conjugation between imino nitrogen and the phenyl group has been lost in *N*-methylamides. Because the electronic stability gain of amide conjugation is more than that of anilide conjugation, the former conjugation was presumably realized at the cost of the latter conjugation to avoid severe steric hindrance between the phenyl ring and the aliphatic group at the carbonyl end. It seems to be of great interest that all of the compounds adopt *cis*-amide structures in spite of that disadvantage. It is obvious that there are no hydrogen-bonding networks to affect the molecular structures in these crystals, different from crystals of free amides. The results of NMR experiments supported the inherent preference of *cis*-amide structures to *trans*-amide in these compounds. Remarkable high-field signal shifts were observed for the C_β protons in the aliphatic groups of *N*-methylanilides, compared with those of the corresponding free anilides: 0.81 and 0.43 ppm for olefinic and 0.30 ppm for methyl protons in **2**, 0.24 ppm for cyclopropyl methylene protons in **3**, 0.23 ppm for protons of the two methyls in **4**, and 0.28 ppm for protons of the three methyls in **5**. These shifts are explained by the *cis*-amide structures, where the alkyl groups are located closely facing the phenyl ring plane.

Regarding the molecular structure of *N*-methylacetanilide (**6**)[7] in the crystal, it has been reported to be cis, in contrast to the trans structure in free acetanilide.[8] The NMR studies clearly supported the *cis*-amide preference in *N*-methylacetanilide in solution.[9]

Thus, it seems to be a general rule that *cis*-amide structure is preferred in *N*-methylamides with an aromatic group at the imino end and with any type of substituent group at the carbonyl end,

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