[9] B. Wrackmeyer, H.-J. Schanz, *Collect. Czech. Chem. Commun.* **1997**, *62*, 1254–1262.

[10] B. Wrackmeyer, H.-J. Schanz, W. Milius, *Angew. Chem.* **1997**, *109*, 98–99; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 75–77.

[11] M. Hofmann, M. A. Fox, R. Greatrex, R. E. Williams, P. von R. Schleyer, *J. Organomet. Chem.*, in press.

[12] B. Wrackmeyer, H.-J. Schanz, W. Milius, *Angew. Chem.* **1997**, *109*, 1145–1147; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1117–1119.

[13] a) T. P. Onak, G. T. F. Wong, *J. Am. Chem. Soc.* **1970**, *92*, 5226; b) V. R. Miller, R. N. Grimes, *Inorg. Chem.* **1972**, *11*, 862–865; c) P. Binger, *Tetrahedron Lett.* **1966**, *24*, 2675–2680; d) P. Binger, *Angew. Chem.* **1968**, *80*, 288–289; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 286; e) M. Herberhold, U. Bertholdt, A. Glöckle, W. Milius, B. Wrackmeyer, *J. Chem. Soc. Chem. Commun.* **1996**, 1219–1220.

[14] R. Köster, G. Seidel, B. Wrackmeyer, D. Bläser, R. Boese, M. Bühl, P. von R. Schleyer, *Chem. Ber.* **1991**, *124*, 2715–2724.

[15] R. N. Grimes, *Adv. Inorg. Chem. Radiochem.* **1983**, *26*, 55–117.

[16] a) P. Jutzi, A. Seufert, *Angew. Chem.* **1977**, *89*, 339–340; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 330; b) C. Dobmeier, R. Köppe, C. Robl, H. Schnöckel, *J. Organomet. Chem.* **1995**, *487*, 127–130.

[17] The discussion of experimental and calculated NMR data of **3** and its derivatives will be reported elsewhere: B. Wrackmeyer, H.-J. Schanz, M. Hofmann, P. von R. Schleyer, unpublished results.

[18] a) A. Fessenbecker, A. Hergel, R. Hettrich, V. Schäfer, W. Siebert, *Chem. Ber.* **1993**, *126*, 2205–2210; b) T. Kuhlmann, H. Pritzkow, U. Zenneck, W. Siebert, *Angew. Chem.* **1984**, *96*, 994–995, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 965–966; c) J. Zwecker, T. Kuhlmann, H. Pritzkow, W. Siebert, U. Zenneck, *Organometallics* **1988**, *7*, 2316–2324.

[19] H. Nöth, B. Wrackmeyer, *NMR Spectroscopy of Boron Compounds*, in *NMR—Principles and Progress, Vol. 14* (Eds.: P. Diehl, E. Fluck, R. Kosfeld), Springer, Berlin, **1978**.

[20] a) M. Bühl, P. von R. Schleyer, *J. Am. Chem. Soc.* **1992**, *114*, 477–491; b) for extensive bibliography, see M. Diaz, J. Jaballas, J. Arias, H. Lee, T. Onak, *J. Am. Chem. Soc.*, **1996**, *118*, 4405–4410.

[21] a) M. A. Fox, R. Greatrex, M. Hofmann, P. von R. Schleyer, R. E. Williams, *Angew. Chem.* **1997**, *109*, 1542–1544; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1498–1501; b) M. Diaz, J. Jaballas, D. Tran, H. Lee, J. Arias, T. Onak, *Inorg. Chem.* **1996**, *35*, 4536–4540, and references therein.

[22] a) The chemical shifts were computed applying the GIAO approach: K. Wolinski, J. F. Hinton, P. Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260; b) M. Häser, R. Ahlrichs, H. P. Baron, P. Weis, H. Horn, *Theor. Chim. Acta* **1992**, *83*, 455–460. The geometries were optimized at the MP2(fc)6-31G* level of theory. The Gaussian 94 program was used throughout: Gaussian 94, Revision D.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W.Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1995**.

[23] C. A. Cupas, L. Hodakowski, *J. Am. Chem. Soc.* **1974**, *96*, 4668–4669.

[24] a) K. Wade, *J. Chem. Soc. Chem. Commun.* **1971**, 792–793; b) K. Wade, *Adv. Inorg. Chem. Radiochem.* **1976**, *18*, 1–67

[25] R. E. Williams, *Adv. Inorg. Chem. Radiochem.* **1976**, *18*, 67–118.

[26] a) J. Bicerano, D. S. Marynick, W. N. Lipscomb, *Inorg. Chem.* **1978**, *17*, 3443–3453. b) M. Gielen *Polyhedron* **1988**, *7*, 363–368.

[27] Fourteen-vertex metallocarboranes are known: W. J. Evans, M. F. Hawthorne, *J. Chem. Soc. Chem. Commun.* **1974**, 38–39; J. R. Pipal, R. N. Grimes, *Inorg. Chem.* **1978**, *17*, 6–10.

Characterization of Hydrogen-Bonded Supramolecular Assemblies by MALDI-TOF Mass Spectrometry after Ag$^+$ Labeling**

Katrina A. Jolliffe, Mercedes Crego Calama, Roel Fokkens, Nico M. M. Nibbering, Peter Timmerman,* and David N. Reinhoudt*

Synthesis based on the formation of noncovalent bonds provides a valuable alternative to the classical chemistry of covalent bonds. It has developed into an area of enormous interest for a wide variety of scientific and technological disciplines, ranging from materials science to molecular electronics.[1, 2] The identification of small hydrogen-bonded dimers[3] or metal-coordinated assemblies[4] is relatively simple. However, for large multicomponent assemblies held together by weak forces the characterization is far from straightforward and is currently one of the major challenges in this field.[5] Most studies primarily rely on NMR data of compounds in solution, which solely provide information on the stoichiometry of the assembly, in combination with data from vapor-pressure osmometry (VPO) and/or gel-permeation chromatography (GPC).[1, 6] The latter techniques give values for the average molecular weight with an error of up to 20%. Occasionally light- or neutron-scattering data[7] or single X-ray crystal structures are reported.[8] However, the characterization of weakly bound noncovalent assemblies by mass spectrometry, the only technique that provides quantitative data on the molecular composition, is still met with very limited success.[9] For hydrogen-bonded assemblies only two cases have been reported by Lehn et al. and Whitesides et al.,[10] but the ion-labeling methods they use either require covalent attachment of benzo[18]crown-6 moieties to one of the components or work only for extremely stable assemblies.

Here we describe a novel Ag$^+$-labeling technique for the mass spectrometric characterization of multicomponent hydrogen-bonded assemblies. The method is based on the remarkably high affinity of Ag$^+$ ions for a variety of aromatic π donors[11, 12] and cyano groups,[13] and it provides for a nondestructive way to generate positively charged hydrogen-bonded assemblies that can be easily detected by matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry.[14] The method is applicable to assemblies of both high (type **A**) and much lower thermodynamic stability (type **B**; Figure 1). Moreover, we show that the MALDI-TOF-MS data perfectly correlate with ^{1}H NMR

---

[*] Dr. P. Timmerman, Prof. Dr. Ir. D. N. Reinhoudt, Dr. K. A. Jolliffe, Dr. M. Crego Calama
Laboratory of Supramolecular Chemistry and Technology
University of Twente
PO Box 217, NL-7500 AE Enschede (The Netherlands)
Fax: (+33) 53-489-4645
E-mail: smct@ct.utwente.nl

R. Fokkens, Prof. Dr. N. M. M. Nibbering
Institute of Mass Spectrometry, University of Amsterdam (The Netherlands)

[**] We thank the European Community for the Marie Curie Research Training Grant (M.C.C., no. ERBFMBICT 961445) as part of the TMR Programme.

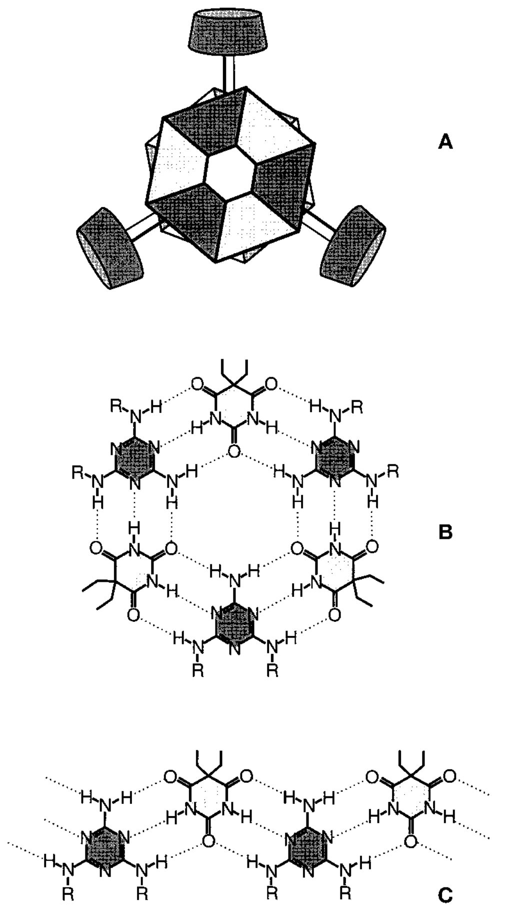


Figure 1. Hydrogen-bonded assemblies with varying thermodynamic stabilities: the cyclic nine-component (type **A**), the cyclic six-component (type **B**), and the linear nondefined assemblies (type **C**).

spectroscopic data on the stability of these assemblies in solution.[8d, 15]

First we studied the nine-component calix[4]arene-based assemblies **A**, which are thermodynamically stable in chloroform even at a concentration of 10^{-4} M.[8a, 15] All attempts to characterize assemblies of type **A** either by electrospray (ES) or MALDI-TOF mass spectrometry have so far been unsuccessful.[10b, 16] However, samples prepared by stirring assemblies of type **A** with 1.5 equivalents of $AgCF_3COO$ in chloroform for at least 24 hours[17] show intense signals for the corresponding Ag^+ complexes in the MALDI-TOF mass spectrum in the case of benzyl-substituted melamine derivatives (assembly **A1**) or cyano-substituted melamine derivatives (assemblies **A4**–**A6**) (Table 1). For example, assembly **A1** (R^2 = benzyl) gives a signal at $m/z = 4278.3$ (calcd for $^{13}C_2{}^{12}C_{226}H_{276}N_{48}O_{30}\cdot{}^{107}Ag^+$: 4276.1, Figure 2a), while assem-

Table 1. MALDI-TOF-MS data for the hydrogen-bonded assemblies **A1**–**A6** and **B1**–**B9**.[a]

Assembly	Molecular composition	Stability in CH_3Cl[b]	Calcd mass [Da] of the Ag complex[c]	Observed mass [Da]
A1	$\mathbf{1}_3\cdot\mathbf{5}_6$	++	4276.1	4278.3
A2	$\mathbf{2}_3\cdot\mathbf{5}_6$	++	4072.0	–
A3	$\mathbf{3}_3\cdot\mathbf{5}_6$	++	4342.0	–
A4	$\mathbf{2}_3\cdot\mathbf{6}_6$	++	4347.9	4348.1
A5	$\mathbf{3}_3\cdot\mathbf{6}_6$	++	4618.8	4620.4
A6	$\mathbf{4}_3\cdot\mathbf{5}_6$	++	4221.9	4220.0
B1	$\mathbf{7}_3\cdot\mathbf{5}_3$	+	1831.9	1831.0
B2	$\mathbf{7}_3\cdot\mathbf{8}_3$	+[d]	1919.0	1919.1
B3	$\mathbf{7}_3\cdot\mathbf{9}_3$	+	4947.4	4947.9
B4	$\mathbf{7}_3\cdot\mathbf{10}_3$	+	3692.2	3692.0
B5	$\mathbf{11}_3\cdot\mathbf{5}_3$	+	1828.4	1828.9
B6	$\mathbf{11}_3\cdot\mathbf{8}_3$	+	1916.0	1915.0
B7	$\mathbf{11}_3\cdot\mathbf{12}_3$	+	2475.2	2476.9
B8	$\mathbf{13}_3\cdot\mathbf{5}_3$	–	1495.3	–
B9	$\mathbf{14}_3\cdot\mathbf{5}_3$	–	1375.3	–

[a] After treatment with 1.5 equivalents of $AgCF_3COO$ for 24 h at room temperature. [b] The notation "+ +" means that the assembly is stable above concentrations of 10^{-4} M, "+" means that the assembly is stable at concentrations above 10^{-2} M, and "–" means that the assembly is not stable in solution. [c] The calculated isotopic patterns are in good agreement with the experimentally observed molecular mass signals. [d] The ^1H NMR spectrum shows a complex pattern for the cyanurate NH protons ($\delta \approx 14$–16), which suggests that the cyclic hexameric assemblies aggregate with themselves.

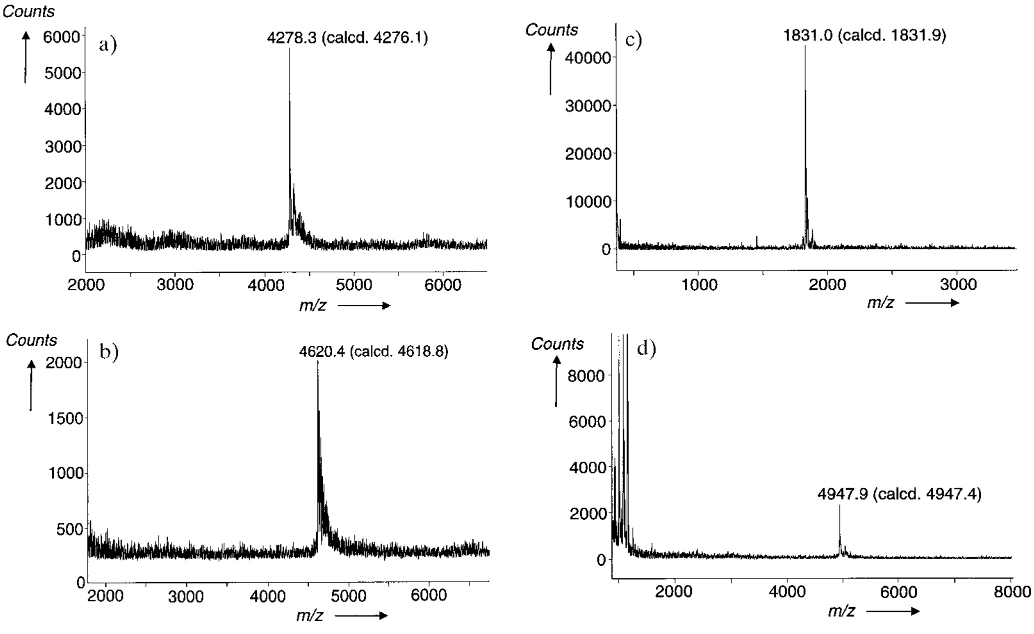


Figure 2. MALDI-TOF mass spectra of the Ag^+ complexes of a) **A1** [$\mathbf{1}_3\cdot\mathbf{5}_6$], b) **A5** [$\mathbf{3}_3\cdot\mathbf{6}_6$], c) **B1** [$\mathbf{7}_3\cdot\mathbf{5}_3$], and d) **B3** [$\mathbf{7}_3\cdot\mathbf{9}_3$].

1433-7851/98/3709-1248 $ 17.50+.50/0

blies **A2** and **A3** (R^2 = butyl) do not show any significant signals between m/z = 1500 and 8000.[18] This clearly indicates that the benzyl group is essential and contributes significantly to the stability of the **A1**·Ag^+ complex, presumably by forming a sandwich-type complex with one of the aromatic rings of the calix[4]arene (Figure 3a).

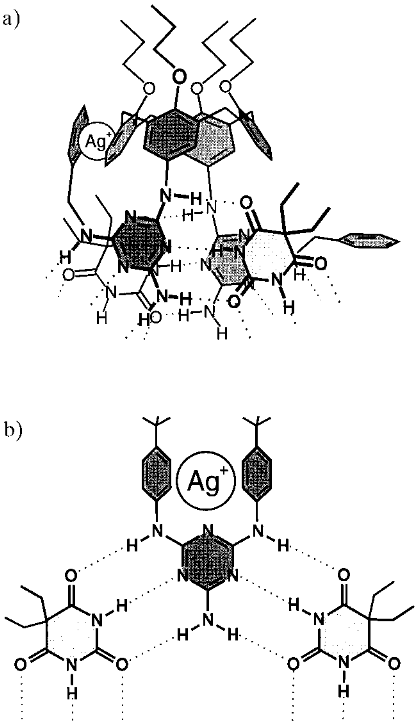
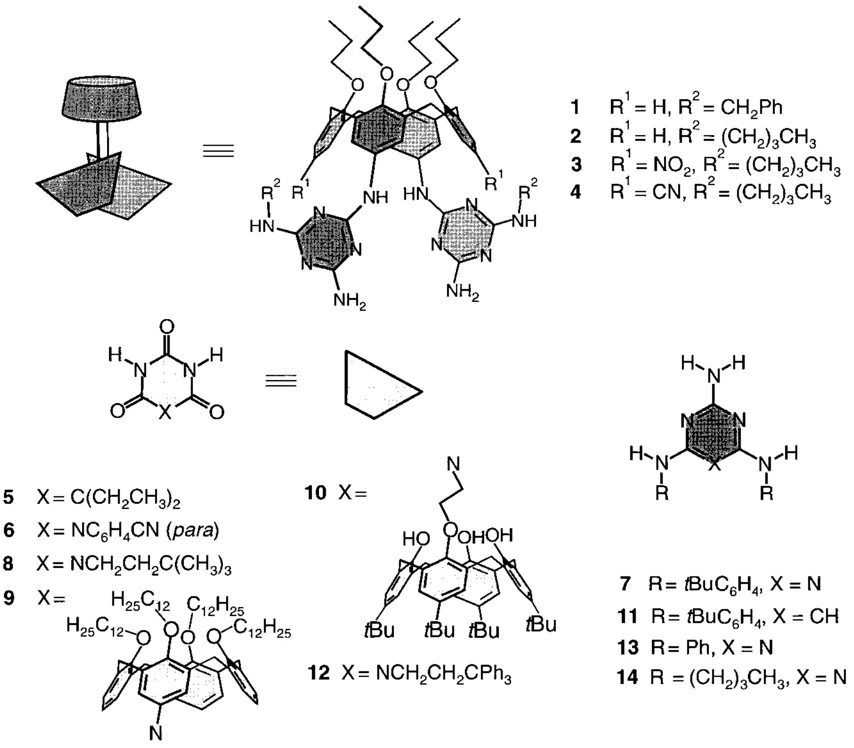


Figure 3. Proposed structure for the Ag^+ complexes of a) **A1** [$1_3 \cdot 5_6$] and b) **B1** [$7_3 \cdot 5_3$] (only parts of the total assemblies are shown for clarity).

For the MALDI-TOF-MS characterization of the hydrogen-bonded assemblies without benzyl groups, formation of the Ag^+ complexes can be promoted by introducing cyano substituents, which are known to have an extremely high affinity for Ag^+ ions.[13] Samples prepared by stirring assemblies **A4** and **A5**, containing the cyano-substituted cyanurate derivative **6**, with 1.5 equivalents of $AgCF_3COO$ in chloroform for at least 24 hours give intense signals in the MALDI-TOF spectra at m/z = 4348.1 (calcd for $^{13}C_2{}^{12}C_{220}H_{252}N_{60}O_{30} \cdot {}^{107}Ag^+$: 4347.9) and 4618.8 (calcd for $^{13}C_2{}^{12}C_{220}H_{246}N_{66}O_{42} \cdot {}^{107}Ag^+$: 4620.4; Figure 2b), respectively, for the monovalent Ag^+ complexes. Alternatively, cyano substituents can be introduced in the calix[4]arene component, as in **4**. Also in this case the monovalent Ag^+ complex of assembly **A6** was clearly observed in the MALDI-TOF spectrum at m/z = 4220.0 (calcd for $^{13}C_2{}^{12}C_{214}H_{282}N_{54}O_{30} \cdot {}^{107}Ag^+$: 4221.9), confirming the formation of **A6** in solution observed with ^1H NMR spectroscopy.[8a]

To test the applicability of the Ag^+-labeling technique for the characterization of assemblies with much lower thermodynamic stability, we studied assemblies of type **B** made from three molecules of melamine **7** with equimolar amounts of either **5** or monosubstituted cyanurates **8**–**10** and **12**.[13] These assemblies are thermodynamically stable in chloroform only at a concentration greater than 10 mM, and their characterization by MALDI-TOF-MS has so far not been successful.[10b, c] In the literature there is only one example of a crown ether derivatized assembly of type **B** that has been characterized with ion-labeling ES-MS.[10a] The MALDI-TOF-MS Ag^+-labeling technique described here clearly identified the hexameric assemblies **B1**–**B7** as the corresponding Ag^+ complexes (see Table 1 for experimental data). For example, assembly **B1** gives a very sharp and intense signal at m/z = 1831.0 (calcd for $C_{93}H_{126}N_{24}O_9 \cdot {}^{107}Ag^+$: 1831.9). Signals corresponding to the doubly or triply charged assemblies **B1**·$(Ag^+)_2$ (m/z = 970.5) or **B1**·$(Ag^+)_3$ (m/z = 682.6) or fragmented assemblies were not observed (Figure 2c). Also the MALDI-TOF spectra of assemblies with high molecular weight such as **B3**, consisting of three molecules of **7** and three molecules of the calix[4]arene derivative **9**, cleanly show a signal for the monovalent Ag^+ complex at m/z = 4947.9 (calcd for $^{13}C_3{}^{12}C_{303}H_{453}N_{27}O_{21} \cdot {}^{107}Ag$: 4947.4). This is the only significant signal in the spectrum between m/z = 2000 and 8000 (Figure 2d). Melamines without bulky substituents (e.g. **13** and **14**) only give linear type **C** assemblies of nondefined composition with equimolar amounts of the complementary barbiturate **5**. MALDI-TOF mass spectra of samples obtained by stirring these assemblies with $AgCF_3COO$ did not show any appreciable signals for the cyclic hexameric assemblies **B8** and **B9**. This is fully in agreement with their



1 R^1 = H, R^2 = CH_2Ph
2 R^1 = H, R^2 = $(CH_2)_3CH_3$
3 R^1 = NO_2, R^2 = $(CH_2)_3CH_3$
4 R^1 = CN, R^2 = $(CH_2)_3CH_3$

5 X = $C(CH_2CH_3)_2$
6 X = NC_6H_4CN (*para*)
8 X = $NCH_2CH_2C(CH_3)_3$
9 X =
10 X =
12 X = $NCH_2CH_2CPh_3$

7 R = tBuC_6H_4, X = N
11 R = tBuC_6H_4, X = CH
13 R = Ph, X = N
14 R = $(CH_2)_3CH_3$, X = N

inherently low stability in solution according to ^{1}H NMR spectroscopy.[8d]

The stable Ag^+ adducts of the assemblies clearly result from the simultaneous coordination of the Ag^+ ion to the aromatic π systems of the *tert*-butylphenyl groups (Figure 3b). Only the phenyl-substituted melamines **7** and **13** give intense signals in the MALDI-TOF mass spectrum for the corresponding Ag^+ complexes ($m/z = 497$ and 385, respectively), while melamine **14** (carrying two butyl chains) or barbiturate **5** do not. It is most likely that the phenyl groups form a sandwich-type complex with the Ag^+ ion. Coordination of the Ag^+ ion to the triazine ring nitrogen atom does not seem to play an important role, because pyrimidine **11** (lacking this nitrogen atom) also shows a strong signal for the corresponding Ag^+ complex ($m/z = 495.7$).

We conclude that MALDI-TOF-MS after Ag^+ labeling is a convenient new tool for the mass spectrometric characterization of hydrogen-bonded assemblies. The absence of any signal corresponding to fragments of assemblies of type **A** or **B** in the mass spectrometer illustrates the unprecedented mildness of the technique. The method requires only a binding site for the soft Ag^+ ion in order to charge the noncovalent assembly in a nondestructive way. Aromatic π donors, which can sandwich a Ag^+ ion, or cyano groups are adequate for this purpose, but in principle many other functionalities such as acetylenes, ethylenes, amines, and sulfur groups may interact strongly with Ag^+ ions.[19] These and other Ag^+ ionophores are quite common in supramolecular systems. Therefore, we feel that MALDI-TOF-MS after Ag^+ labeling might provide a method of general interest as a MS characterization technique for noncovalent assemblies or host–guest complexes.

Experimental Section

Samples were prepared by stirring solutions of assemblies **A1**–**A6** and **B1**–**B9** in $CHCl_3$ (5–10 mM) with solid $AgCF_3COO$ (1.5 equiv per assembly, ACROS, 98% purity) for 24 h and mixing an aliquot of this solution (10 μL) with an aliquot (30 μL) of a solution of 2,5-dihydroxybenzoic acid (3 mg L^{-1}) in $CHCl_3$. A portion (1 μL) of the resulting solution was loaded on a gold-sample plate, the solvent removed in warm air, and the sample transferred to the mass spectrometer for analysis.

The hydrogen-bonded assemblies of type **A** and **B** were identified by MALDI-TOF-MS[14] using a PerSeptive Biosystems Voyager-DE-RP MALDI-TOF mass spectrometer (PerSeptive Biosystems, Inc., Framingham, MA, USA) equipped with delayed extraction.[20] A 337-nm UV nitrogen laser producing 3-ns pulses was used, and the mass spectra were obtained in the linear and reflectron mode. Mass assignments were performed with unmanipulated spectra (no smoothing or centering, etc.) for an optimal correlation between observed and calculated mass.

Received: October 30, 1997 [Z11105IE]
German version: *Angew. Chem.* **1998**, *110*, 1294–1297

Keywords: hydrogen bonds · mass spectrometry · noncovalent interactions · supramolecular chemistry

---

[1] G. M. Whitesides, E. E. Simanek, J. P. Mathias, C. T. Seto, D. N. Chin, M. Mammen, D. M. Gordon, *Acc. Chem. Res.* **1995**, *28*, 37–44, and references therein.

[2] Recent reviews on this topic: a) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1668; b) B. Linton, A. D. Hamilton, *ibid.* **1997**, *97*, 1669–1680; c) D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242–1286; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154–1194; d) D. S. Lawrence, T. Jiang, M. Levett, *Chem. Rev.* **1995**, *95*, 2229–2260.

[3] a) R. M. Grotzfeld, N. Branda, J. Rebek, Jr., *Science* **1996**, *271*, 487–489; b) B. C. Hamann, K. D. Shimizu, J. Rebek, Jr., *Angew. Chem.* **1996**, *108*, 1425–1427; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1326–1329; c) O. Mogck, M. Pons, V. Böhmer, W. Vogt, *J. Am. Chem. Soc.* **1997**, *119*, 5706–5712.

[4] a) P. Jacopozzi, E. Dalcanale, *Angew. Chem.* **1997**, *109*, 665–667; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 613–615; b) D. P. Funeriu, J.-M. Lehn, G. Baum, D. Fenske, *Chem. Eur. J.* **1997**, *3*, 99–104; c) W. T. S. Huck, F. C. J. M. van Veggel, D. N. Reinhoudt, *Angew. Chem.* **1996**, *108*, 1304–1306; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1213–1215; d) M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi, K. Ogura, *Nature* **1995**, *378*, 469–471.

[5] W. T. S. Huck, R. Hulst, P. Timmerman, F. C. J. M. van Veggel, D. N. Reinhoudt, *Angew. Chem.* **1997**, *109*, 1006–1008; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1046–1049.

[6] a) S. Tirumala, J. T. Davis, *J. Am. Chem. Soc.* **1997**, *119*, 2769–2776; b) M. Mammen, E. E. Simanek, G. M. Whitesides, *ibid.* **1996**, *118*, 12614–12623; c) J. L. Sessler, R. Wang, *ibid.* **1996**, *118*, 9808–9809; d) A. Marsh, M. Silvestri, J.-M. Lehn, *Chem. Commun.* **1996**, 1527–1528; e) C. M. Drain, K. C. Russell, J.-M. Lehn, *ibid.* **1996**, 337–338; f) J. P. Mathias, E. E. Simanek, G. M. Whitesides, *J. Am. Chem. Soc.* **1994**, *116*, 4326–4340.

[7] a) S. C. Zimmerman, F. Zeng, D. E. C. Reichert, S. V. Kolotuchin, *Science* **1996**, *271*, 1095–1098; b) P. Thiyagarajan, F. Zeng, C. Y. Ku, S. C. Zimmerman, *J. Mater. Chem.* **1997**, *7*, 1221–1226.

[8] a) P. Timmerman, R. H. Vreekamp, R. Hulst, W. Verboom, D. N. Reinhoudt, K. Rissanen, K. A. Udachin, J. Ripmeester, *Chem. Eur. J.* **1997**, *3*, 1823–1832; b) M. Mascal, N. M. Hecht, R. Warmuth, M. H. Moore, J. P. Turkenburg, *Angew. Chem.* **1996**, *108*, 2348–2350; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2204–2206; c) A. Zafar, J. Yang, S. J. Geib, A. D. Hamilton, *Tetrahedron Lett.* **1996**, *37*, 2327–2330; d) J. P. Mathias, E. E. Simanek, J. A. Zerkowski, C. T. Seto, G. M. Whitesides, *J. Am. Chem. Soc.* **1994**, *116*, 4316–4325.

[9] Review: M. Vincenti, *J. Mass Spectrom.* **1995**, *30*, 925–939.

[10] a) K. C. Russell, E. Leize, A. van Dorsselaer, J.-M. Lehn, *Angew. Chem.* **1995**, *107*, 244–248; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 209–213; b) X. Cheng, Q. Gao, R. D. Smith, E. E. Simanek, M. Mammen, G. M. Whitesides, *J. Org. Chem.* **1996**, *61*, 2204–2206; c) *Rapid Commun. Mass Spectrom.* **1995**, *9*, 312–316.

[11] a) H. C. Kang, A. W. Hanson, B. Eaton, V. Boekelheide, *J. Am. Chem. Soc.* **1985**, *107*, 1979–1985; b) J. Gross, G. Harder, F. Vögtle, H. Stephan, K. Gloe, *Angew. Chem.* **1995**, *107*, 523–526; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 481–484.

[12] a) A. Ikeda, H. Tsuzuki, S. Shinkai, *J. Chem. Soc. Perkin Trans. 2* **1994**, 2073–2080; b) O. Struck, L. A. J. Chrisstoffels, R. J. W. Lugtenberg, W. Verboom, G. J. van Hummel, S. Harkema, D. N. Reinhoudt, *J. Org. Chem.* **1997**, *62*, 2487–2493.

[13] *Gmelin Handbuch der Anorganischen Chemie*, *Silber*, *Teil B6*, Springer, Berlin, **1975**, pp. 346–353.

[14] a) M. Karas, D. Bachmann, U. Bahr, F. Hillenkamp, *Int. J. Mass Spectrom. Ion Processes* **1987**, *78*, 53–68; b) F. Hillenkamp, M. Karas, *Anal. Chem.* **1991**, *63*, 1193A–1203A.

[15] R. H. Vreekamp, M. Hubert, J. P. M. van Duynhoven, W. Verboom, D. N. Reinhoudt, *Angew. Chem.* **1996**, *108*, 1306–1309; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1215–1218.

[16] We tested the Cl^--labeling ES-MS technique for various different assemblies of type **A** without success. This is agreement with the results found by the group of Whitesides.[10b]

[17] The use of 4.0 equivalents of $AgCF_3COO$ leads to complete destruction of the assemblies.

[18] It is quite remarkable that assemblies **A2** and **A3** do not form stable Ag^+ complexes by themselves, since calix[4]arenes are known to interact strongly with Ag^+ ions through the aromatic π faces at the upper rim of the cavity.[12] This is confirmed by the presence of intense signals for the Ag^+ complexes of calix[4]arenes **2** and **3** in the MALDI-TOF mass spectra. Apparently, the calix[4]arene skeleton loses its affinity for Ag^+ ions upon formation of the hydrogen-bonded assembly. This is most probably a consequence of the extreme conformational change that the calix[4]arene skeleton undergoes when the hydrogen-bonded assembly is formed. The X-ray crystal

structure of assembly **A3** reveals that the melamine-substituted aromatic ring carbon atoms are 4.05 Å apart,[8a] which is 0.75 Å less than the optimal distance measured from the crystal structure of the calix[4]arene–Ag^+ complex.[12a] Formation of the hydrogen-bonded assembly therefore leaves too little space for complexation of the Ag^+ ions in between the parallel aromatic rings of the calix[4]arene fragment.

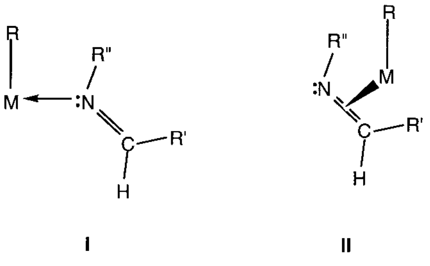
[19] General overview of functional groups that interact with Ag^+ ions: *Gmelin Handbuch der Anorganischen Chemie*, *Silber*, *Teil B5–B7*, Springer, Berlin, **1975**.

[20] M. L. Vestal, P. Juhasz, S. A. Martin, *Rapid Commun. Mass Spectrom.* **1995**, *9*, 1044–1050.

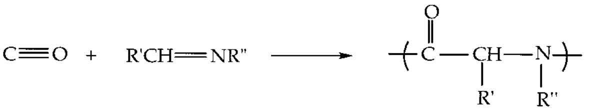
Insertion of Imines into Palladium–Acyl Bonds: Towards Metal-Catalyzed Alternating Copolymerization of Imines with Carbon Monoxide To Form Polypeptides**

Smita Kacker, Jang Sub Kim, and Ayusman Sen*

The insertion of unsaturated molecules into metal–carbon bonds is a critically important step in many transition-metal-catalyzed organic transformations. In particular, the insertion of alkenes and alkynes into metal–carbon bonds resulting in carbon–carbon bond formation has been extensively studied.[1] However, the analogous insertion of compounds with carbon–nitrogen multiple bonds has received far less attention: this is particularly true of imines.[2] The difference in insertion propensity of carbon–carbon and carbon–nitrogen multiple bonds can be attributed to the coordination characteristics of the respective molecules. Alkenes and alkynes form π-complexes with metals. For imines, σ-donation of the lone pair of electrons on the nitrogen is the preferred mode of interaction with the metal center (for example, structure **I**).[3] Since migratory insertion must be preceded by π coordination (structure **II**), the difficulty in achieving σ to π isomerization may be the reason for the paucity of imine insertions.[2] Herein we report the synthesis of amides by the insertion of imines into palladium(II)–acyl bonds. To our knowledge, this is the first direct observation of the insertion of imines into bonds between transition metals and carbon. The interest in this chemistry lies in the potentially new route to carbon–nitrogen bond formation. In particular, the alternating copolymerization of imines with carbon monoxide (in which the insertion of the imine into palladium–acyl bonds would be the key step in the chain growth sequence), if successful, should constitute a new procedure for the synthesis of polypeptides [Eq. (1)].[4]



(R, R', R'' = H, alkyl, aryl)



$$C{\equiv}O + R'CH{=}NR'' \longrightarrow \left(\overset{\overset{\displaystyle O}{\|}}{C} - \underset{\underset{\displaystyle R'}{|}}{CH} - \underset{\underset{\displaystyle R''}{|}}{N} \right) \tag{1}$$

Neutral palladium(II)–methyl complexes incorporating a range of bidentate phosphane and nitrogen ligands reacted with silver tetrafluoroborate in the presence of imines to form the corresponding imine-coordinated cationic complexes **1a–k** in excellent yields. The compound **1a** (L–L = 1,3-bis(diphenylphosphanyl)propane) was isolated as a solid consisting of 91 % $\mathbf{1a}\cdot Et_2O$ and 9 % [(dppp)$PdCl_2$] (the composition was determined by a combination of ^1H and ^{31}P NMR spectroscopy). A satisfactory elemental analysis (C,H) was obtained for a mixture of this composition. The complexes **1a–k** were found to be stable for over one month under nitrogen; there was no evidence of insertion of imine into the palladium–methyl bond.

The imine ligand was coordinated to the metal by σ donation of the lone pair of electrons on nitrogen (structure **I**). This was established from the ^1H and ^{13}C NMR spectra of the complexes. For example, in the ^1H NMR spectrum of complex **1c** (L–L = dppp, R = PhCH=NBz), recorded in $CDCl_3$, the CH protons of the coordinated imine appeared at $\delta = 8.20$ (dd, $J = 2$, 7.4 Hz) compared with $\delta = 8.29$ for the CH protons of the noncoordinated imine. The corresponding carbon appeared at $\delta = 167.89$ in the $^{13}C\{^1H\}$ NMR ($CDCl_3$) spectrum compared with $\delta = 160.69$ for the noncoordinated imine. On the other hand, π complexation has been shown to result in significant upfield shifts of these resonances.[3b]

The reactivity of complexes **1a–k** towards carbon monoxide was examined by exposing them to an atmosphere of carbon monoxide at ambient temperature and a pressure of 3.4 bar. The results are summarized in Scheme 1. All the complexes reacted with carbon monoxide to form the corresponding palladium(II)–acyl species. However, the stability of these palladium–acyl species varied greatly. These complexes (**2**) could only be observed when the subsequent insertion of the imine into the palladium–acyl bond was slow or did not occur. ^{13}C-labeled carbon monoxide was used to facilitate characterization of the products: complexes formed with ^{13}CO are marked with an asterisk (*).

For complexes with nitrogen-donor ligands **1i–k** the corresponding palladium(II)–acyl complexes **2i–k** were formed in 16 h. The ^{13}C NMR resonance due to the carbonyl of the acyl group was observed at $\delta \approx 232$ for **2i*–k*** as is typical for palladium(II)–acyl complexes.[5] There was no

---

[*] Prof. Dr. A. Sen, Dr. S. Kacker, Dr. J. S. Kim
Department of Chemistry
The Pennsylvania State University
University Park, PA 16802 (USA)
Fax: (+1) 814-863-8403
E-mail: asen@chem.psu.edu

[**] This research was supported by a grant from the US Department of Energy, Office of Basic Energy Sciences