

Ordering of Ruthenium Cluster Carbonyls in Mesoporous Silica

Wuzong Zhou,* John Meurig Thomas,* Douglas S. Shephard, Brian F. G. Johnson, Don Ozkaya, Thomas Maschmeyer, Robert G. Bell, Qingfeng Ge

The anionic ruthenium cluster carbonylates $[\text{Ru}_6\text{C}(\text{CO})_{16}]^{2-}$ or $[\text{H}_2\text{Ru}_{10}(\text{CO})_{25}]^{2-}$ interspersed with bis(triphenylphosphino)iminium counterions (PPN^+) are incorporated from solution into the pores of MCM-41 mesoporous silica (3 nanometers in diameter), where they form tightly packed arrays. These arrays were shown by high-resolution transmission electron microscopy, Fourier transform optical diffraction, and computer simulations to be well ordered both along and perpendicular to the axis of the cylindrical pores. In their denuded state produced by gentle thermolysis, the cluster carbonylates yield nanoparticles of ruthenium that are less well ordered than their assimilated precursors but show good activity as hydrogenation catalysts for hexene and cyclooctene. In both their as-prepared and denuded states, these encapsulated clusters are likely to exhibit interesting electronic and other properties.

Finely divided metals have been the subject of scientific investigation since the time of Faraday and earlier (1, 2). They exhibit electronic (3), magnetic (4, 5), thermal (3–5), catalytic (6, 7), optical (8), and other properties that differ from those of the corresponding bulk metals. Mono- and bimetallic nanoparticles (6) in the size range 0.5 to 5 nm have attracted particular interest because of their catalytic properties. Mesoporous molecular sieves such as MCM-41, first reported by Mobil scientists in 1992 (9), are among the best candidates as a support material for metal clusters because of their sizable pores, ranging from 1.5 nm to >10 nm.

We recently proposed that nanoparticles denuded by gentle thermolysis of the encapsulated carbonylate salts may be attached to the interior surface of the mesoporous silica and may exhibit promising catalytic properties in the hydrogenation of alkenes (10, 11). Given the scope that exists in controlling the population of the cluster carbonylates within the mesopores

of the siliceous host, interesting electronic, optical, and sensor properties may also be expected. In this previous work, we introduced $[\text{Ag}_3\text{Ru}_{10}\text{C}_2(\text{CO})_{28}\text{Cl}][\text{PPN}]_2$ and $[\text{Ru}_{12}\text{C}_2\text{Cu}_4(\text{CO})_{32}\text{Cl}_2][\text{PPN}]_2$ salts into the MCM-41 channels and measured the catalytic performance of the denuded salts (that is, the bimetallic nanoparticles) for the hydrogenation of hex-1-ene and a range of other alkenes (10, 11). The nanoclusters were shown to be disordered in the channels (10, 11).

In view of the general interest in the properties of nanoelectronic materials, much effort has recently been expended (12) in the development of novel ways of producing ordered arrays, including linked cluster networks, of metallic nanoparticles in a size range down to ~1.5 nm. As part of our program (13) to design and synthesize well-defined solid catalysts derived from MCM-41 and organometallic precursors, we herein report an effective method of producing highly ordered one-dimensional (1D) arrays of Ru cluster carbonylates [such as those described in (14)] inside the 3-nm-

diameter mesopores of MCM-41 silica. To our knowledge, the only prior comparable preparation of linear arrays of metallic nanoparticles [apart from “decorated” atomic steps on graphite (15) and molybdenite (16) surfaces with nanoparticles of the coinage metals and the insertion of materials inside carbon nanotubes (17)] is that of Schmid and Hornyak (4), who recently reported that the 50-nm-diameter pores of alumina membranes could be packed with 13-nm-diameter, ligand-stabilized Au_{55} colloids by vacuum induction.

The silanol groups that line the mesopores of the silica facilitate the uptake of the bulky cluster anions by hydrogen bonding with the carbonyl groups of the guest species (10). We synthesized and characterized the two salts $[\text{Ru}_6\text{C}(\text{CO})_{16}][\text{PPN}]_2$ and $[\text{H}_2\text{Ru}_{10}(\text{CO})_{25}][\text{PPN}]_2$, henceforth designated **I** and **II** (18), and tested the maximum degree of incorporation of **I** or **II** into the silica as follows. The silica and either **I** or **II** were made into a slurry in ether and a small amount of a second solvent, dichloromethane (CH_2Cl_2) (19). The maximum loadings for the two cluster salts, expressed as mass salt per mass MCM-41, are 8:7 for **I** and 15:9 for **II** (20).

We are confident that the cluster salts **I** and **II** are each assimilated intact by the MCM-41 for three reasons. First, each of the salts may be completely recovered by solvent extraction from the mesopores. Second, parallel extended x-ray absorption fine structure studies that we have carried out (10, 11) on analogous cluster carbonylate salts, $[\text{Ag}_3\text{Ru}_{10}\text{C}_2(\text{CO})_{28}\text{Cl}][\text{PPN}]_2$ and $[\text{Ru}_6\text{C}(\text{CO})_{16}\text{Cu}_2\text{Cl}_2][\text{PPN}]_2$, taken up by MCM-41 show that the x-ray absorption spectra of the dispersed and assimilated clusters are indistinguishable (21). Third, microanalysis (C, H, N) results were in accordance with the loadings as prepared.

The infrared (IR) spectroscopic profiles of the CO stretching vibrations of clusters **I** and **II** assimilated by the MCM-41 are much more complex than those of the same clusters in CH_2Cl_2 solution [single absorp-

W. Zhou, D. S. Shephard, B. F. G. Johnson, Q. Ge, University Chemical Laboratories, Lensfield Road, Cambridge CB2 1EW, UK.

J. M. Thomas, Davy-Faraday Research Laboratories, Royal Institution of Great Britain, 21 Albemarle Street, London W1X 4BS, UK, and Department of Materials Science, University of Cambridge, Pembroke Street, Cambridge CB2 3QZ, UK.

D. Ozkaya, Department of Materials Science, University of Cambridge, Pembroke Street, Cambridge CB2 3QZ, UK.

T. Maschmeyer, University Chemical Laboratories, Lensfield Road, Cambridge CB2 1EW, UK, and Davy-Faraday Research Laboratories, Royal Institution of Great Britain, 21 Albemarle Street, London W1X 4BS, UK.

R. G. Bell, Davy-Faraday Research Laboratories, Royal Institution of Great Britain, 21 Albemarle Street, London W1X 4BS, UK.

*To whom correspondence should be addressed. E-mail: wz100@cus.cam.ac.uk (W.Z.)

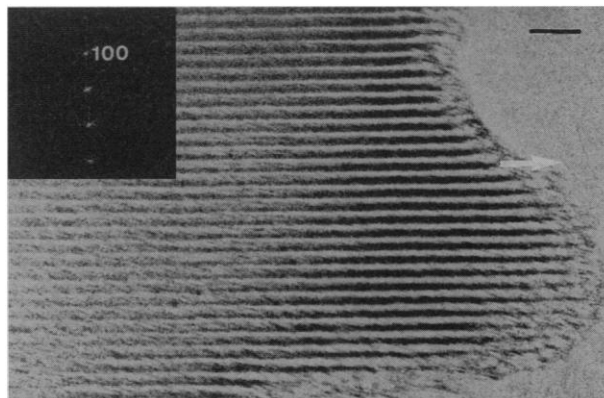


Fig. 1. HRTEM image of pure silica MCM-41, with its Fourier transform (inset), viewed perpendicular to the pore axis ([001] direction, indicated by the arrow). Scale bar, 10 nm.

Fig. 2. HRTEM image of MCM-41 loaded with $[\text{Ru}_6\text{C}(\text{CO})_{16}][\text{PPN}]_2$ (I), with its Fourier transform (inset). The average repeat distance derived from the reciprocal space (002) spots of the Fourier transform is ~ 2.1 nm, corresponding to a projection of the average repeat distance on the [001] axis for the clusters. The black dots lie along the pore axis, forming a rosary-like pattern, and the arrow indicates the area showing interchannel ordering of the beads. Scale bar, 10 nm.

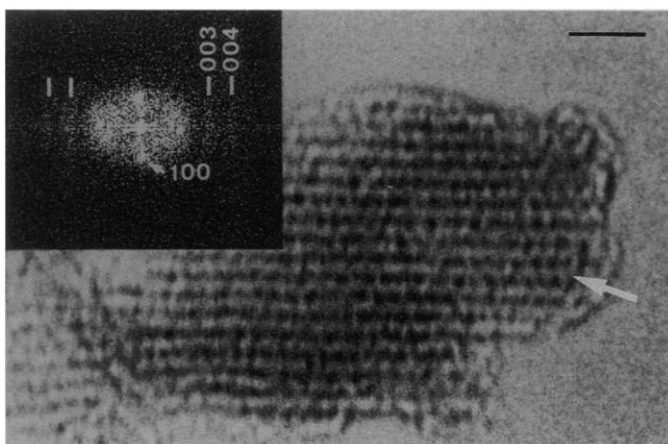


Fig. 3. STEM bright-field image (24) of MCM-41 loaded with $[\text{H}_2\text{Ru}_{10}(\text{CO})_{25}][\text{PPN}]_2$ (II) showing highly regular features along the pore axis, with its Fourier transform (inset). The repeat distance derived from the reciprocal space (001) spots of the Fourier transform is ~ 2.95 nm. Scale bar, 20 nm.

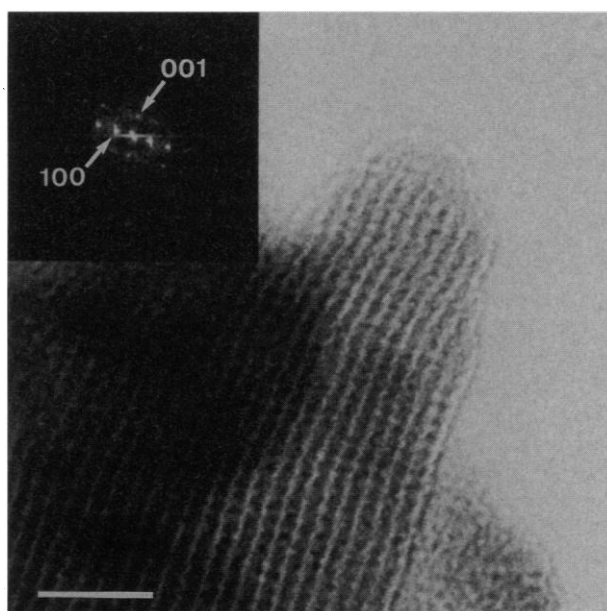
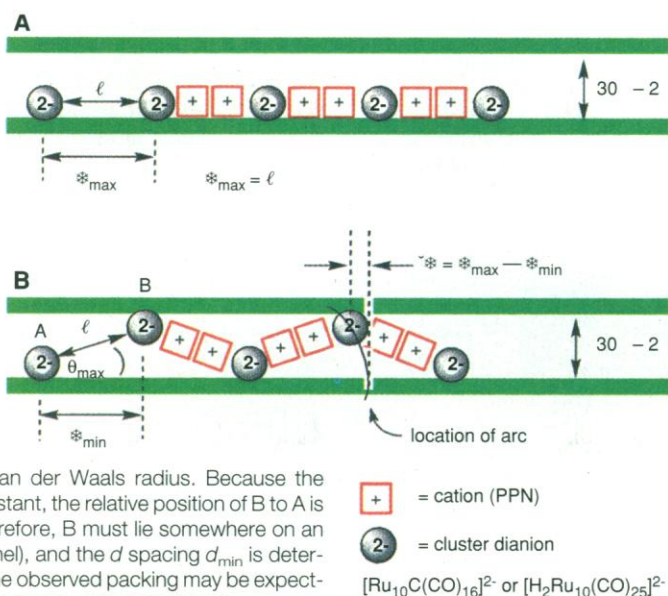


Fig. 4. A schematic diagram showing how the maximum and minimum d spacings can be derived from geometrical packing considerations. It is assumed that the clusters are separated by two PPN cations, that they are connected by their van der Waals surfaces, and that the internal pore diameter is 3 nm. (A) Packing that gives the maximum d spacing d_{max} ; (B) packing that gives the minimum d spacing for a cluster carbonyl of given van der Waals radius. Because the intercluster spacing ℓ is constant, the relative position of B to A is determined by angle θ . Therefore, B must lie somewhere on an ellipse (in a cylindrical channel), and the d spacing d_{min} is determined by $d_{\text{min}} = \ell(\cos \theta)$. The observed packing may be expected to lie within the limits $0 \leq \theta \leq \theta_{\text{max}}$ for constant ℓ .



tion maxima at 1977 cm^{-1} and 2010 cm^{-1} for I and II, respectively (14)]. Moreover, the main absorption peak shifts to lower energy, indicating that the interaction between the carbonylate species and the silanols is quite strong.

High-resolution transmission electron microscopy (HRTEM) images (22, 23) show the regular nature of the mesopores of the MCM-41 silica (Fig. 1), and the 1D diffraction pattern along the [100] direction indicates that there is no crystallographic ordering along the axis of the empty mesopores. In contrast, the HRTEM image of I loaded into the MCM-41 (Fig. 2) shows many black dots partially ordered along the pore axis, forming a "rosary"-like pattern. In agreement with this partial ordering, a few arced diffraction lines are observed in the Fourier transform ("optical" diffractogram) of this image (Fig. 2, inset). From both the real space image and the reciprocal space (diffraction) pattern, an average repeat distance (~ 2.1 nm in real space) is obtained. A scanning transmission electron microscopy (STEM) image of the MCM-41 loaded with II (Fig. 3) displays a regular repeat distance along the pore axis [001] of ~ 2.95 nm, and this is also in agreement with the corresponding Fourier transform of the STEM image (24).

Interpretation of the features seen in Figs. 2 and 3 is facilitated by the known crystal structures and packing motifs (x-ray derived) of pure I and II (14). In each case the carbonylate cluster anion is associated with two $[\text{PPN}^+]$ cations, and the center-to-center distances between adjacent ions are, for I, ~ 0.93 nm from $[\text{Ru}_6\text{C}(\text{CO})_{16}]^{2-}$ to PPN^+ and, for II, ~ 1.06 nm from $[\text{H}_2\text{Ru}_{10}(\text{CO})_{25}]^{2-}$ to PPN^+ and 0.80 nm from PPN^+ to its adjacent PPN^+ . In MCM-41-I, the individual hexaruthenate clusters are hydrogen-bonded to the pore wall (through interactions of the type $\text{Si}-\text{O}-\text{H} \cdots \text{O}-\text{C}-\text{Ru}$) and are flanked by two PPN^+ counterions. If the $\text{PPN}^+[\text{Ru}_6\text{C}(\text{CO})_{16}]^{2-}\text{PPN}^+$ triads were lined up as in pure crystals of I along the mesopore axis, the distances between two Ru_6 clusters would be ~ 2.7 nm (2×0.93 nm + 0.8 nm) (Fig. 4A). But the observed separation is only ~ 2.1 nm (Fig. 2), and thus the "linear packing" mode is clearly not adopted. However, if a cluster situated within a mesopore is separated by two PPN^+ ions with a constant interaction distance of ~ 2.7 nm, then a second cluster may be readily accommodated at any point on an ellipse within a cylindrical channel (Fig. 4B), thereby yielding a projected distance between two adjacent clusters in the mesopore that is considerably less than in the idealized, linear model. Given that the observed center-to-center distance between two hexaruthenate

clusters is 2.1 nm, that the van der Waals diameter of the cluster is ~ 1.1 nm, and that the pore diameter is 3.0 nm, we conclude that the clusters pack in a zigzag fashion with an operative angle of 39° .

In MCM-41-II, the observed average intercluster distance (deduced from the diffraction patterns and the HRTEM images) is 2.95 nm, not too dissimilar to the ideal intercluster distance of 2.92 nm found in crystals of pure II (see Fig. 5). Therefore, in the case of the larger diameter decaruthenate clusters, the packing mode adopted within the mesopores is linear.

The micrographs of both MCM-41-I and MCM-41-II display not only the rosary-like arrangement of dots along the pore axis but also a strong tendency for alignment of the dots in directions inclined to the pore axes; this is especially marked in MCM-41-I. The intrachannel ordering of the guest ions is predominantly governed by a combination of molecular recognition, pore-wall interaction, and electrostatic considerations, whereas the interchannel ordering requires a directing force that permeates through the pore walls of the siliceous host (~ 0.6 nm thick). We believe, though it remains to be tested, that two of the attributes of the cluster anions (but not of the PPN^+ counterions)—namely electrostatic charge and an aptitude to form multiple hydrogen bonds with the pore walls—will introduce some elastic strain that will, through the packing of the ruthenate ions, introduce periodicity in the elastic strain energy that will be felt by other clusters in

adjacent channels. This is the likely reason for the observed 3D ordering.

Computer simulations using the multislice procedure (25) on both empty MCM-41 and MCM-41-II covering a wide range

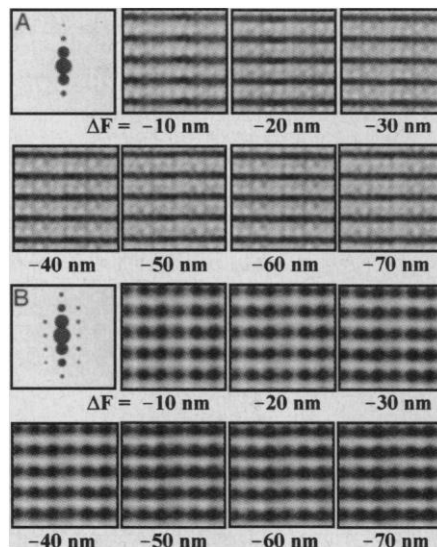


Fig. 6. Computer simulations of electron diffraction patterns and images viewed down the [100] direction using models of (A) pure MCM-41 and (B) MCM-41 loaded with $[\text{H}_2\text{Ru}_{10}(\text{CO})_{25}][\text{PPN}]_2$. Specimen thicknesses are 40.7 nm; lens defocus values ΔF are indicated. Calculations were carried out for a range of specimen thickness from 3.7 to 55.5 nm and lens defocus from 0 to -160 nm. These simulations establish conclusively that the observed ordering in the HRTEM images results from the ordering of the metal clusters.

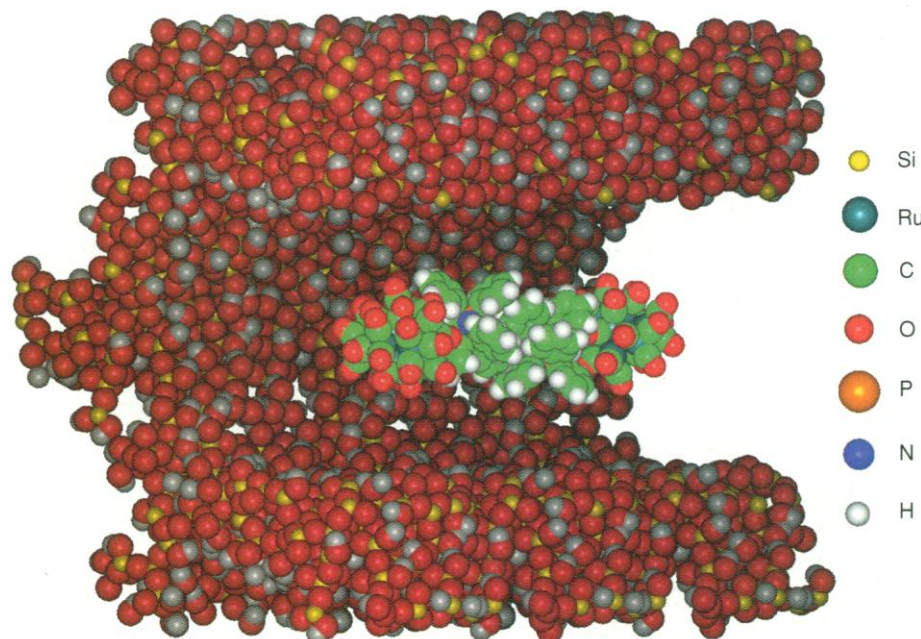


Fig. 5. Van der Waals surface interactions of two $[\text{H}_2\text{Ru}_{10}(\text{CO})_{25}]^{2-}$ and two PPN^+ molecules packing along a single mesopore. These coordinates were the basis for the simulated electron diffraction patterns and HRTEM images.

of specimen thickness and lens defocus reproduced both the 1D electron diffraction patterns and the images of Figs. 1 and 3 (Fig. 6) (26). The size of the dots in the experimental images (Figs. 2 and 3) is larger than the real size of the ruthenate clusters (which can be judged from Fig. 5) because of lattice vibration at the finite temperature of the electron microscopy.

Although much work remains to be done on these constrained arrays of monodisperse nanoparticles, many applications can be readily envisaged. Our preliminary experiments on the denuded ruthenate clusters (effected by gentle heating in vacuo at 180°C for 1 hour) show that the resulting nanoparticles of ruthenium, which are somewhat less ordered along the pore axis than are their precursors, display promising catalytic activity in the hydrogenation of alkenes (27). The hydrogenation of hex-1-ene by MCM-41- Ru_{10} (particles ~ 1.3 nm in diameter) was studied in a batch reactor at 120°C , and there was essentially complete conversion to *n*-hexane. The hydrogenation of an internal alkene, *cis*-cyclooctene, by MCM-41- Ru_6 at room temperature also proceeded to completion and the kinetic data showed no evidence of limitations. Given that it appears feasible to prepare aligned films of MCM-41 (28) and that other metal carbonylates are readily available, it is clear that many reductions and oxidations [of the type described by Felthouse *et al.* (29)] may be catalytically effected by the type of catalysts described herein.

REFERENCES AND NOTES

1. M. Faraday, *Philos. Trans. R. Soc.* **147**, 145 (1857).
2. J. M. Thomas, *Rev. Pure Appl. Chem.* **60**, 1517 (1988) and references therein.
3. Y. Valokitin, J. Sinzig, L. J. DeJongh, G. Schmid, I. I. Moiseev, *Nature* **384**, 621 (1997).
4. G. Schmid and G. L. Hornyak, *Curr. Opin. Solid State Mat. Sci.* **2**, 204 (1997).
5. G. Georgiadis, V. A. Self, P. A. Sermon, *Angew. Chem. Int. Ed. Engl.* **26**, 1042 (1987); A. Simon, *ibid.* **27**, 159 (1988).
6. J. H. Sinfelt, *Bimetallic Catalysts, An Exxon Monograph* (Wiley, New York, 1983).
7. H. Kuroda and Y. Iwasawa, *Int. Rev. Phys. Chem.* **8**, 207 (1989); J. H. Sinfelt, *ibid.* **7**, 281 (1988); M. Che and C. O. Bennet, *Adv. Catal.* **36**, 55 (1989); T. Yamamoto and I. Shido, *J. Am. Chem. Soc.* **118**, 5810 (1996).
8. A. Henglein, *Isr. J. Chem.* **33**, 77 (1993).
9. C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **359**, 710 (1992); J. S. Beck *et al.*, *J. Am. Chem. Soc.* **114**, 10835 (1992).
10. D. S. Shephard *et al.*, *Angew. Chem. Int. Ed. Engl.* **36**, 2242 (1997).
11. D. S. Shephard *et al.*, *Chem. Eur. J.*, in press; T. Fujii and K. Toriomi, *J. Chem. Soc. Faraday Trans.* **89**, 3437 (1993).
12. M. Brust, D. Bethell, D. J. Schiffrin, C. J. Kiely, *Adv. Mater.* **7**, 795 (1995); R. L. Whetten *et al.*, *ibid.* **8**, 428 (1996); R. P. Andres *et al.*, *Science* **273**, 1690 (1996); A. P. Alivisatos *et al.*, *Nature* **382**, 609 (1996).
13. T. Maschmeyer, F. Rey, G. Sankar, J. M. Thomas, *Nature* **378**, 159 (1995); T. Maschmeyer *et al.*, *Angew. Chem. Int. Ed. Engl.* **36**, 1639 (1997); J. M.

- Thomas, *Faraday Discuss. R. Soc. Chem.* **105**, 1 (1996); *Chem. Eur. J.* **3**, 1557 (1997).
14. B. F. G. Johnson *et al.*, *J. Organomet. Chem.* **191**, C3 (1980); P. J. Bailey *et al.*, *J. Chem. Soc. Dalton Trans.* **1996**, 3515 (1996).
 15. J. M. Thomas, E. L. Evans, J. O. Williams, *Proc. R. Soc. London Ser. A* **331**, 417 (1972); G. M. Francis, I. M. Goldby, L. Kuipers, B. Vonissendorff, R. E. Palmer, *J. Chem. Soc. Dalton Trans.* **1996**, 665 (1996).
 16. O. P. Bahl, E. L. Evans, J. M. Thomas, *Surf. Sci.* **8**, 473 (1967).
 17. J. Sloan, J. Cook, M. L. H. Green, J. L. Hutchison, R. Tenne, *J. Mater. Chem.* **7**, 1089 (1997).
 18. All reactions were carried out under exclusion of air using solvents freshly distilled under an atmosphere of nitrogen. IR spectra were recorded on a Perkin-Elmer 1600 series Fourier transform IR spectrometer in CH_2Cl_2 using NaCl cells or a Nujol mull. Negative fast ion bombardment mass spectra were obtained using a Kratos MS50TC spectrometer, with CsI as calibrant. Separation of products was accomplished with Merck thin layer chromatography plates as supplied (0.25-mm layer of Kieselgel 60 F254). $[\text{Ru}_6\text{C}(\text{CO})_{16}][\text{PPN}]_2$, $[\text{H}_2\text{Ru}_{10}(\text{CO})_{25}][\text{PPN}]_2$, and MCM-41 were prepared by literature procedures (14).
 19. Ether and CH_2Cl_2 were found to be the most effective of several combinations. The small amount of CH_2Cl_2 is thought to ferry the cluster salt through the liquid phase to the silica surface; upon contact with the surface, the (predominantly) CH_2Cl_2 solvation shell is substituted by the silanol groups. The solvent molecules enable repetition of this cycle: Entropy change provides the driving force for the anions to enter the mesopores by way of substituting for loosely held solvent molecules, whereas the drop in enthalpy directs the ordering of the sorbed clusters onto the pore walls.
 20. MCM-41 powder (200 mg) was dried under high vacuum (0.01 mm Hg) at 473 K for 6 hours. This was then slurried with dry ether (30 ml) and I or II along with CH_2Cl_2 (0.1 ml) at ambient temperature in the absence of light for 72 hours. The resulting red or brown solid was washed with ether (10 ml) and dried under high vacuum (0.01 mm Hg). Spectroscopic data for MCM-41- Ru_6 : IR (Nujol): $\nu(\text{CO})$ 2056 (w), 1968 (vs), 1929 (m, sh), 1910 (m), 1816 (w, sh), 1795 (w), 1727 (s) cm^{-1} . Spectroscopic data for MCM-41- Ru_{10} : IR (Nujol): $\nu(\text{CO})$ 2053 (m), 2044 (w, sh), 2007 (vs), 1989 (s, sh), 1955 (s, sh), 1931 (s), 1780 (w), 1751 (w), 1709 (w) cm^{-1} (w, weak; m, medium; s, strong; vs, very strong; sh, shoulder).
 21. Similar experiments at the Synchrotron Source (Daresbury Lab, UK) will soon be carried out on MCM-41, I and II (D. S. Shephard and G. Sankar, in preparation).
 22. D. A. Jefferson *et al.*, *Nature* **323**, 428 (1986); G. R. Millward and J. M. Thomas, in *Proceedings of Carbon and Graphite Conference* (Society of Chemical Industry, London, 1974), pp. 492–497.
 23. HRTEM images were recorded with a JEOL JEM-200CX electron microscope operating at 200 kV with a modified specimen stage with objective lens parameters $C_s = 0.41$ mm and $C_o = 0.95$ mm, giving an interpretable point resolution of ~ 0.185 nm. STEM experiments were conducted using a field emission dedicated microscope (VG HB501). MCM-41 samples were prepared by crushing the particles between two glass slides and spreading them on a holey carbon film supported on a Cu grid. The samples were briefly heated under a tungsten filament light bulb in air before transfer into the specimen chamber. The images were recorded at magnifications of 24,000 $\times$ to 49,000 $\times$.
 24. Although STEM images display less contrast than the corresponding HRTEM images, STEM enables shorter exposure times, hence electron-beam damage is reduced.
 25. D. A. Jefferson *et al.*, *Nature* **281**, 51 (1979).
 26. The hexagonal MCM-41 model with a framework based on silica glass structures was modeled by molecular dynamics [B. Vessal, M. Amini, D. Fincham, *J. Non-Cryst. Solids* **159**, 184 (1993)]. The channel volume was excised from the glass structure, and the resulting dangling bonds were satisfied

by H (to O) or by OH (to Si). The unit cell parameters are $a = 3.703$ nm and $c = 7.98$ nm. The pore wall thickness is ~ 0.6 nm. The resulting periodic structure was optimized by energy minimization with the program Discover [version 4.0.0; Molecular Simulations Inc., San Diego, CA (1996)] with the cff91_ozco force field [J. R. Hill and J. Sauer, *J. Phys. Chem.* **98**, 1238 (1994)] and later with the program GULP [General Utility Lattice Program; J. D. Gale, Royal Institution and Imperial College, London (1991)]. Three clusters of $[\text{H}_2\text{Ru}_{10}(\text{CO})_{25}][\text{PPN}]_2$ were loaded with an intercluster distance of 2.66 nm.

27. For hydrogenation of hex-1-ene, a 150-ml Teflon-lined autoclave equipped with a magnetic follower was charged with 8.2 mg of MCM-41- Ru_{10} , 3.0 ml of hex-1-ene, and H_2 at 65 atm. After heating to 393 K for 4 hours, the vessel was cooled to ambient temperature and the contents analyzed by ^1H NMR to reveal $>99\%$ conversion to *n*-hexane. A subsequent run was performed with 12 ml of hex-1-ene to establish the turnover frequency (TOF). This gave 15% conversion to hex-2-ene and 50% conversion to hexane, yielding a TOF of 4400-mol[Hex]/mol[Ru_{10}] $^{-1}$ hour $^{-1}$. For hydrogenation of *cis*-cyclooctene, a 250-ml Erlenmeyer flask equipped with a magnetic follower was charged with ~ 10 mg of

MCM-41- Ru_6 , 10 ml of *cis*-cyclooctene, and H_2 at 1 atm. The flask was kept at 298 K for 72 hours, during which time the contents were analyzed by ^1H NMR and gas chromatography-mass spectrometry. The analysis showed a steady conversion to cyclooctane; no unconverted starting material was detected after 72 hours. From these results, an overall TOF of ~ 130 mol[Cyclo- C_8]/mol[Ru_6] $^{-1}$ hour $^{-1}$ was calculated.

28. M. E. Raimondi, T. Maschmeyer, R. H. Templer, J. M. Seddon, *J. Chem. Soc. Chem. Commun.* **1997**, 1843 (1997).
29. T. R. Felthouse *et al.*, in *Advanced Catalysts and Nanostructured Materials: Modern Synthetic Methods*, W. R. Mozar, Ed. (Academic Press, San Diego, CA, 1996), pp. 91–115.
30. Supported by an Engineering and Physical Sciences Research Council (UK) rolling grant (J.M.T.), postdoctoral research award (B.F.G.J.), a European Union (EU) TMR award (B.F.G.J.), an EU Fellowship TMR (T.M.), the University of Cambridge, and the Royal Society for the Smithsonian Research Fellowship (Peterhouse) (D.S.S.). W.Z. thanks D. A. Jefferson for many helpful discussions.

6 January 1998; accepted 5 March 1998

A Trivalent System from Vancomycin-D-Ala-D-Ala with Higher Affinity Than Avidin-Biotin

Jianghong Rao, Joydeep Lahiri, Lyle Isaacs, Robert M. Weis, George M. Whitesides*

Tris(vancomycin carboxamide) binds a trivalent ligand derived from D-Ala-D-Ala with very high affinity: dissociation constant (K_d) $\approx 4 \times 10^{-17} \pm 1 \times 10^{-17}$ M. High-affinity trivalent binding and monovalent binding are fundamentally different. In trivalent (and more generally, polyvalent) binding, dissociation occurs in stages, and its rate can be accelerated by monovalent ligand at sufficiently high concentrations. In monovalent binding, dissociation is determined solely by the rate constant for dissociation and cannot be accelerated by added monomer. Calorimetric measurements for the trivalent system indicate an approximately additive gain in enthalpy relative to the corresponding monomers. This system is one of the most stable organic receptor-ligand pairs involving small molecules that is known. It illustrates the practicality of designing very high-affinity systems based on polyvalency.

Polyvalent inhibitors can be used for blocking the adhesion of pathogens to the surfaces of target cells (1, 2). The enhanced biological activity observed in these systems has been rationalized in terms of the roles of enthalpy and entropy. Similar strategies using polyvalency may also be applied to other problems in biochemistry such as blocking carbohydrate-protein interactions and controlling cellular signal transduction (3–7). We describe the design and synthesis of a trivalent system of receptor and ligand derived from vancomycin and D-Ala-D-Ala (DADA), respectively, that shows exceptionally high affinity [its binding constant

(K_d) is $\sim 4 \times 10^{-17} \pm 1 \times 10^{-17}$ M, 25 times tighter than biotin-avidin, which is one of the strongest interactions known in biological systems (8)] and we characterize the thermodynamics and kinetics of this high-affinity system.

We chose the vancomycin-DADA pair for elaboration into a polyvalent system for five reasons: (i) vancomycin is relatively rigid, and there is little loss in conformational entropy on binding (Table 1) (9); (ii) Williams and others have studied it in detail structurally (10–12) and thermodynamically (9, 13); (iii) the two components are readily available and relatively easily modified synthetically (7); (iv) the monovalent complex has a convenient binding constant ($K_d \approx 1 \mu\text{M}$) (14); and (v) Williams proposed that noncovalent divalency is important in the binding of vancomycin to DADA groups in bacterial cell walls (15–17).

The design of the trivalent vancomycin

J. Rao, J. Lahiri, L. Isaacs, G. M. Whitesides, Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, MA 02138, USA.
R. M. Weis, Department of Chemistry, University of Massachusetts, Amherst, MA 01003, USA.

* To whom correspondence should be addressed. E-mail: gwhitesides@gmwhgroup.harvard.edu