Observation of reaction intermediates and kinetic mistakes in a remarkably slow self-assembly reaction†

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Several intermediates and oligomeric mistakes in a metal–ligand self-assembly reaction are identified by ^{1}H NMR, MALDI-MS, and XRD, providing evidence in support of multiple pathways in the "free-for-all" self-assembly process.

Self-assembly is the most efficient route to prepare discrete supramolecules,[1,2] but the complexity of the dynamic self-assembly process is still poorly understood.[3] It is generally accepted that this process involves the correction of misconnections and random oligomeric errors, quickly leading from kinetic intermediates to the discrete, thermodynamic product. Despite this widespread assumption, there exist only a few examples of the observation of oligomeric errors ("kinetic mistakes") and in these cases they are not structurally characterized.[4] Additional examples involving the observation of self-assembly intermediates exist, but because most of these reactions between metals (M) and organic ligands (L) occur spontaneously and quickly, it is difficult to observe kinetic intermediates that form prior to the final thermodynamic product.[5] Intermediates have been observed during the titration of one component (M or L) into the other, but this approach is limited in that only the *equilibrium* product of each titration is observed in solution.[6,7] Rarely are kinetic intermediates stable enough to isolate from solution.[7,8]

Since the speed by which self-assembly reactions occur precludes the observation of intermediates and kinetic mistakes, slowing down the process could allow a better understanding of metal-directed assembly. This may ultimately lead to the ability to incorporate design features and specific properties into supramolecular assemblies with more predictability. Paradoxically, for the self-assembly of discrete species to occur in a reasonable amount of time, fast kinetics are required in the forming and breaking of individual supramolecular interactions (typically either labile metal–ligand bonds or H-bonds). In this communication, we describe the relatively slow self-assembly of M_2L_2 supramolecular macrocycles. This reaction occurs over the course of several days which allows for the observation and identification of several intermediate species and "kinetic mistakes" along the pathway to macrocycle formation.

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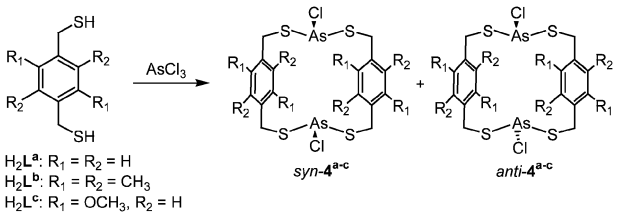


Scheme 1 Ligands and $As_2L_2Cl_2$ macrocycles.[11]

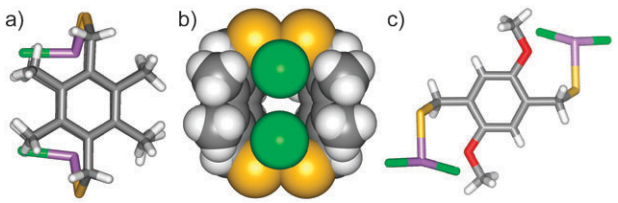


Fig. 1 X-Ray crystal structure representations of (a) $As_2(\mathbf{L^b})_2Cl_2$ (stick), (b) $As_2(\mathbf{L^b})_2Cl_2$ (van der Waals radii), and (c) $As_2\mathbf{L^c}Cl_4$ (stick).

A mixture of *syn*- and *anti*-$As_2L_2Cl_2$ macrocycles forms in solution over the course of several days (Scheme 1) when rigid dithiol ligands $H_2\mathbf{L^a}$,[9] $H_2\mathbf{L^b}$ and $H_2\mathbf{L^c}$[10] are individually treated with arsenic trichloride. X-Ray quality crystals of *syn*-$As_2\mathbf{L^b}_2Cl_2$ were grown by diffusion of pentane into a solution of $As_2\mathbf{L^b}_2Cl_2$ in chloroform. The crystal structure (Fig. 1a and b) reveals an As–As distance of 4.45 Å and a distance of 4.26 to 7.45 Å between the methyl carbons on opposite ligands, leaving a small cavity that is devoid of a guest.

When $As_2\mathbf{L^a}_2Cl_2$ (**4^a**) and $As_2\mathbf{L^b}_2Cl_2$ (**4^b**) are prepared in d-chloroform, the reaction progress can be monitored by observing the changes to the methylene region of the ^{1}H NMR spectrum (Fig. 2 for **4^a** and Fig. S1 (ESI†) for **4^b**). In each case, as H_2L is consumed, its resonances are replaced with those corresponding to several different reaction intermediates. These, in turn, are replaced with the resonances for **4**, the fully formed macrocycles. While several of the methylene region resonances overlap, it was possible to identify three of these intermediate species by symmetry. The first species observed upon treatment of H_2L with $AsCl_3$ is $HL(AsCl_2)$ (**1**), which appears as a doublet for the unbound (CH_2SH) end and a singlet for the bound ($CH_2S(AsCl_2)$) end. The next observed species is HL(AsCl)LH (**2**) which appears as an ABq for the bound ($(CH_2S)_2AsCl$) end and a doublet for the unbound (CH_2SH) end, which is coincidental with the resonance for H_2L or **1**. The third species that can be identified by ^{1}H NMR is $L(AsCl_2)_2$ (**3**), which appears downfield as a singlet since the ligand symmetrically spans two As centers.

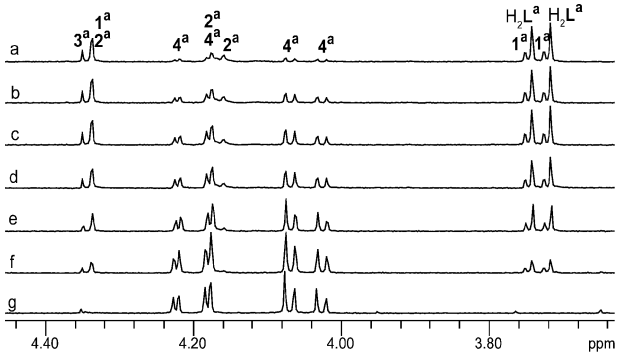
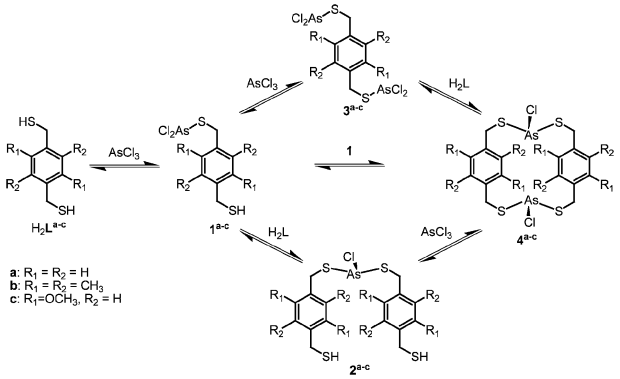


Fig. 2 CH_2 region of ^1H NMR spectra of reaction of H_2L^a with $AsCl_3$ after (a) 35, (b) 81, (c) 122, (d) 186, (e) 366, (f) 1378, and (g) 5650 minutes. Structures of $\mathbf{1^a}$–$\mathbf{4^a}$ are shown in Scheme 2.



Scheme 2 Self-assembly of $As_2L_2Cl_2$.

The identities of $\mathbf{1^b}$–$\mathbf{4^b}$ were also confirmed by MALDI-MS ($[\mathbf{1^b} + Na + 2H]^+$, 394.9, calc. 394.9; $[\mathbf{2^b} + Na + 4H]^+$, 587.0, calc. 587.1; $[\mathbf{3^b} + Na]^+$, 536.8, calc. 536.8; $[\mathbf{4^b} + Na]^+$, 690.9, calc. 690.9), when $As_2L_2Cl_2$ was prepared from $H_2\mathbf{L^b}$.† These species could either be intermediates or kinetic mistakes that are corrected in the self-assembly of $As_2L_2Cl_2$ (**4**). It is possible that the self-assembly reaction is occurring simultaneously through several competing pathways as outlined in Scheme 2.[12]‡

While the overlapping resonances of H_2L, **1**, **2**, **3**, and $As_2L_2Cl_2$ (**4**) make it difficult to accurately integrate the NMR spectra, it is clear that at least one additional discrete species exists in solution,[13] likely a larger oligomeric "kinetic mistake". These kinetic mistakes could easily form reversibly in the free-for-all chaos of the self-assembly reaction and then equilibrate to $As_2L_2Cl_2$. After 5 minutes, and under the same conditions as the NMR experiments, several oligomeric species (Chart 1) were identified by MALDI-MS ($[\mathbf{5^b} + Na + 2H]^+$, 728.9, calc. 728.9; $[\mathbf{6^b} + Na]^+$, 870.7, calc. 870.7; $[\mathbf{7^b} + Na + 4H]^+$, 921.0, calc. 921.0; $[\mathbf{8^b} + Na + 2H]^+$, 1062.8, calc. 1062.9; $[\mathbf{9^b} + Na]^+$, 1206.7, calc. 1204.7).† These species could be expected to have ^1H NMR resonances that overlap with the other intermediates. We do not know for sure that every one of these oligomeric species is present in solution during the reaction, as they could be formed as a concentration effect upon evaporation of the MALDI sample, yet after 30 minutes they are no longer observed by MALDI. It is clear that some kinetic mistakes

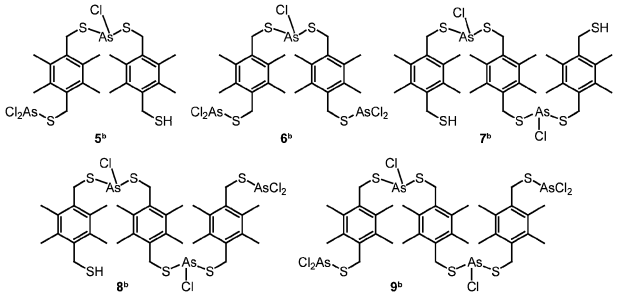


Chart 1 Oligomeric kinetic mistakes.

are corrected during the course of the reaction because everything remains soluble and all resonances except those for $As_2L_2Cl_2$ disappear eventually. These oligomeric species observed by MALDI-MS are the most likely culprits.

The isolation of compounds **1–3** was unsuccessful until prepared from a ligand with additional coordinating groups (methyl ether in $H_2\mathbf{L^c}$). While macrocycle was typically isolated by crystallization of the reaction mixture of $H_2\mathbf{L^c}$ and $AsCl_3$,[10] one attempt led to the isolation of $\mathbf{3^c}$ (Fig. 1c). The intermediate is stabilized by As–O secondary bonding interactions[14] and crystal packing is dictated by the As–π interaction.[15] This experiment further supports the idea that structure **3** is an intermediate or a kinetic mistake in the self-assembly of $As_2L_2Cl_2$ (Scheme 2).

In conclusion, we have shown a metal-directed self-assembly reaction in which several intermediates and kinetic mistakes can be identified. This provides insight into the complexity of the self-assembly process—as revealed by the multiple possible pathways—even for a simple dinuclear species. While most self-assembly reactions occur too quickly to observe without stopped flow kinetics, the dynamic covalent[16] nature of the As–S bond and the steric bulk of the ligands make this reaction slow enough to observe by ^1H NMR, providing exquisite structural detail. This shows that supramolecular chemistry based on main group elements not only leads to new structure types,[17] but also can add valuable insight into the nature of self-assembly, which could be applicable to understanding the formation of nanoparticles,[18] polymers[19] and monolayers[20] by self-assembly.

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Notes and references

‡ Unfortunately the slow kinetics and complexity of the reaction do not allow for the measurement of rate constants. EXSY NMR experiments were carried out on the reaction of $AsCl_3$ with a monofunctional model ligand (2-mercaptomethylnaphthalene) at 120 °C, but no ligand exchange was observed.

1 C. Piguet, G. Bernardinelli and G. Hopfgartner, *Chem. Rev.*, 1997, **97**, 2005; M. Albrecht, *Chem. Rev.*, 2001, **101**, 3457; M. Elhabiri and A. M. Albrecht-Gary, *Coord. Chem. Rev.*, 2008, **252**, 1079.

2 R. W. Saalfrank, H. Maid and A. Scheurer, *Angew. Chem., Int. Ed.*, 2008, **47**, 8794; S. Leininger, B. Olenyuk and P. J. Stang, *Chem. Rev.*, 2000, **100**, 853; G. F. Swiegers and T. J. Malefetse, *Chem. Rev.*, 2000, **100**, 3483; D. L. Caulder and K. N. Raymond, *J. Chem. Soc., Dalton Trans.*, 1999, 1185.

3 A. V. Davis, R. M. Yeh and K. N. Raymond, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4793; J. M. Lehn, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4763; J. M. Lehn, *Chem. Soc. Rev.*, 2007, **36**, 151.

4 M. Fujita, S. Nagao and K. Ogura, *J. Am. Chem. Soc.*, 1995, **117**, 1649; P. Baxter, J. M. Lehn, A. Decian and J. Fischer, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 69.

5 J. J. Pak, J. Greaves, D. J. McCord and K. J. Shea, *Organometallics*, 2002, **21**, 3552; S. Sato, Y. Ishido and M. Fujita, *J. Am. Chem. Soc.*, 2009, **131**, 6064.

6 A. Pfeil and J. M. Lehn, *Chem. Commun.*, 1992, 838; M. D. Levin and P. J. Stang, *J. Am. Chem. Soc.*, 2000, **122**, 7428; N. Fatin-Rouge, S. Blanc, E. Leize, A. Van Dorsselaer, P. Baret, J. L. Pierre and A. M. Albrecht-Gary, *Inorg. Chem.*, 2000, **39**, 5771; N. Fatin-Rouge, S. Blanc, A. Pfeil, A. Rigault, A. M. Albrecht-Gary and J. M. Lehn, *Helv. Chim. Acta*, 2001, **84**, 1694; A. Marquis, J. P. Kintzinger, R. Graff, P. N. W. Baxter and J. M. Lehn, *Angew. Chem., Int. Ed.*, 2002, **41**, 2760; J. Hamacek, S. Blanc, M. Elhabiri, E. Leize, A. Van Dorsselaer, C. Piguet and A. M. Albrecht-Gary, *J. Am. Chem. Soc.*, 2003, **125**, 1541; M. Elhabiri, J. Hamacek, J. C. G. Bunzli and A. M. Albrecht-Gary, *Eur. J. Inorg. Chem.*, 2004, 51; E. Leize, A. V. Dorsselaer, R. Kramer and J. M. Lehn, *Chem. Commun.*, 1993, 990.

7 N. Takeda, K. Umemoto, K. Yamaguchi and M. Fujita, *Nature*, 1999, **398**, 794.

8 B. Hasenknopf, J. M. Lehn, N. Boumediene, E. Leize and A. Van Dorsselaer, *Angew. Chem., Int. Ed.*, 1998, **37**, 3265; M. Albrecht, S. Dehn and R. Frohlich, *Angew. Chem., Int. Ed.*, 2006, **45**, 2792.

9 W. J. Vickaryous, E. R. Healey, O. B. Berryman and D. W. Johnson, *Inorg. Chem.*, 2005, **44**, 9247.

10 V. M. Cangelosi, L. N. Zakharov, S. A. Fontenot, M. A. Pitt and D. W. Johnson, *Dalton Trans.*, 2008, 3447.

11 Both chlorine atoms are on the same side of the macrocyclic cavity in the *syn* macrocycle and on opposite sides in the anti-macrocycle.

12 **2** and **3** could be both intermediates and kinetic mistakes.

13 The *ABq*s in the ^{1}H NMR corresponding to $\mathbf{2^a}$ and $\mathbf{4^a}$ overlap. However, before the signal for $\mathbf{4^a}$ becomes prominent, the asymmetry of the signal is clear, suggesting an overlapping resonance. The signal for $\mathbf{2^b}$ is clearly an *ABq* (see Fig. S1, ESI†).

14 T. G. Carter, E. R. Healey, M. A. Pitt and D. W. Johnson, *Inorg. Chem.*, 2005, **44**, 9634.

15 H. Schmidbaur and A. Schier, *Organometallics*, 2008, **27**, 2361.

16 S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2002, **41**, 898; V. E. Campbell, X. d. Hatten, N. Delsuc, B. Kauffmann, I. Huc and J. R. Nitschke, *Chem.–Eur. J.*, 2009, **15**, 6138.

17 M. A. Pitt and D. W. Johnson, *Chem. Soc. Rev.*, 2007, **36**, 1441.

18 M. A. Watzky, E. E. Finney and R. G. Finke, *J. Am. Chem. Soc.*, 2008, **130**, 11959.

19 C. Alberto, *Macromol. Rapid Commun.*, 2002, **23**, 511.

20 D. K. Schwartz, *Annu. Rev. Phys. Chem.*, 2001, **52**, 107.

