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A pillar[5]arene with an amino-terminated arm stabilizes the formation of aliphatic hemiaminals and imines

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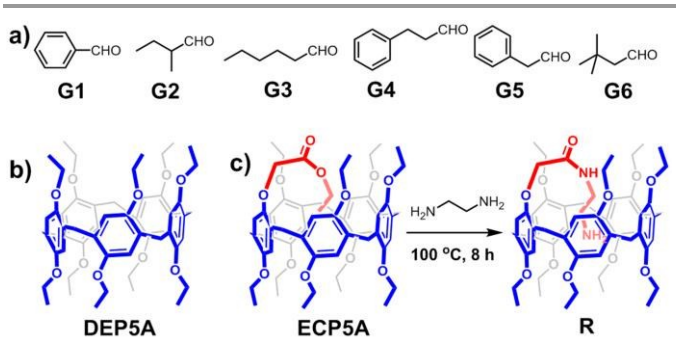
We report a new mono-armed pillar[5]arene with the amino-substituent self-included in the pillarene cavity, which can stabilize the hemiaminals and imines formed from the reaction of aliphatic amines and aldehydes as monitored by mass spectroscopy.

Pillar[n]arenes, first reported by Ogoshi and co-workers in 2008,[1] have advanced significantly and shown many interesting applications in supramolecular assembly,[2-4] advanced functional materials,[5-11] molecular machinery,[12-14] etc.,[15-21] due to the unique rigid cylindrical structure with a particular ring size and an electron-rich cavity, ease and diversity of functionalization, and appreciable host-guest properties. Among them, pillar[5]arene and its derivatives are still the most widely investigated ones partly due to the relatively high yielding of synthesis. Pillar[5]arene can form host–guest inclusion complexes with electron poor species and neutral molecules such as linear alkanes, but not with branched or cyclic alkanes with large steric hindrance.[11,12,22] On the basis of this property, we developed some strategies for the efficient syntheses of mono-ester and bis-ester arm functionalized pillar[5]arene derivatives via a one-pot reaction,[23-25] holding great potentials in the construction of functional materials by facile modification.

On the other hand, imine bond formation is currently one of the most widely used reactions that play a vital role in the dynamic combinatorial (or covalent) chemistry (DCC)[26-34] and macrocyclic chemistry.[35, 36] The process of imine bond formation has generally been considered to occur in a stepwise manner, among which the hemiaminal intermediate has received much attention to help further understand its real mechanism.[37] Some direct observations of active hemiaminals have been reported. For example, Wilson and co-workers observed the hemiaminal intermediates in an enzyme mechanism at an atomic resolution.[38] Fujita and co-workers observed a transient hemiaminal trapped in a porous network *via* X-ray analysis.[39,40] Yaghi and co-workers employed metal-organic frameworks to stabilize hemiaminals.[41] Rebek and co-workers reported the use of macrocycles in the stabilization of hemiaminals,[42,43] and the calculation by Li and co-workers is also of great importance to complement the complexity during the formation of imines.[44] However, it still remains challenging to characterize aliphatic imines and hemiaminals by analytical methods such as electrospray ionization mass spectrum (ESI-MS). To the best of our knowledge, no MS data for aliphatic hemiaminals and imines have ever been reported due to their instability in the conditions of ESI-MS. Thus, we are highly interested in developing a strategy to stabilize aliphatic hemiaminals and imines in the isolated state and trace these active species by ESI-MS.

Inspired by our previous work on the synthesis of a stable functionalized pseudo[1]rotaxane in high yield by the aminolysis of monoester-based copillar[5]arene,[23] we envision that it is of great possibility to find a suitable supramolecular nanoreactor to stabilize the formation of aliphatic hemiaminals and imines by properly functionalizing and optimizing a pillar[5]arene host to endow itself not only a stable self-included structure but also a reactive motif that fully sits in the centre of the cavity. We started with the synthesis of an analogue, ethoxyl-based copillar[5]arene (**ECP5A**),



Scheme 1 Chemical structures of a) the aldehydes and b) **DEP5A**; c) Synthetic route to the nanoreactor (**R**).

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Electronic Supplementary Information (ESI) available: Experimental section, characterization data including ^{1}H NMR spectra, ^{13}C NMR spectra, 2D NMR spectra, mass spectra of related compounds. See DOI: 10.1039/x0xx00000x

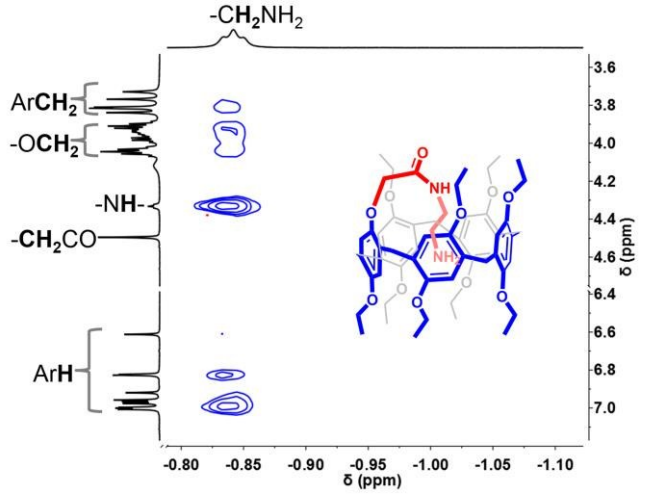

Fig. 1 Partial NOESY spectrum (600 MHz, $CDCl_3$, 298 K) of **R**.

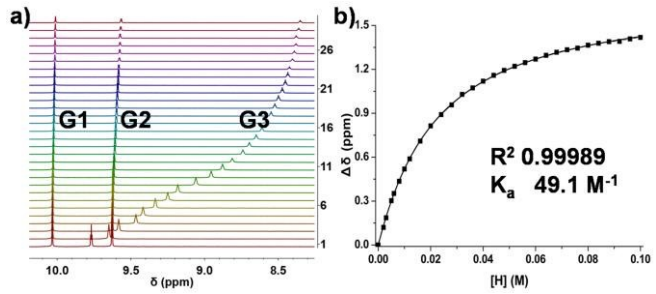

Fig. 2 a) Partial ^{1}H NMR titration spectra (400 MHz, $CDCl_3$, 298 K) of three aldehydes (**G1**, **G2**, and **G3**) at an equal concentration of 4 mM upon addition of **DEP5A**. b) The non-linear curve-fitting for the complexation of **G3** (4 mM) and **DEP5A** in $CDCl_3$ at 298 K.

which was subsequently subjected to solvolysis by ethylenediamine to get **R** (Scheme 1). Interestingly, **DEP5A** (Fig. S3-5, ESI†) as one of the by-products was separated in the one-pot reaction where **ECP5A** was synthesized. **ECP5A** was characterized by ^{1}H and ^{13}C NMR spectroscopy, and mass spectroscopy (Fig. S6-8, ESI†). In its ^{1}H NMR spectrum, the δ_{ppm} values of the ethyl protons belonging to the ester group were upfield shifted to 2.49 (-CH_2-) and -1.30 (-CH_3) in $CDCl_3$ at room temperature, suggesting the presence of a self-included structure. **R** was analysed by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, mass spectroscopy, and 2D NMR spectroscopy including HSQC and NOESY in $CDCl_3$ (Fig. S9-12, ESI†). In Fig. 1, the NOE cross-peaks between –CH_2- that belongs to the ethylenediamine moiety and the backbone protons of the pillar[5]arene suggested that a self-included conformation of **R** in $CDCl_3$, similar to the reported crystals of an analogue of **R**.[45]

Subsequently, some analogous aldehydes have been selected to demonstrate the strategy of dynamic combinatorial libraries (DCLs) that has been widely used in the search of novel systems with astonishing functionalities,[46] because we believe that some representative aryl or branched aldehydes, on the contrary to linear aldehydes, are not able to enter the cavity of **R**. Therefore, three kinds of aldehydes, that is, benzaldehyde (**G1**), 2-methylbutylaldehyde (**G2**), and caproaldehyde (**G3**) were chosen for comparison. As a prototype, **DEP5A** was used as the candidate to evaluate the DCLs. Firstly, the stoichiometry of **DEP5A** (host) and the selected aldehydes (guest) was determined to be 1:1 by Job's plot method (Fig. S13-18, Table S1-3, ESI†). Secondly, the binding constants between hosts and guests have also been investigated. We used a mixture of three aldehydes and **DEP5A** for ^{1}H NMR titration (Fig. 2a). From the non-linear curve-fitting, the binding constant of **G3** and **DEP5A** was calculated to be 49 M^{-1} (Fig. 2b), in accordance with the reported value,[47] and the binding constant between **G1** (or **G2**) and **DEP5A** was too small to be measured (Fig. S19-20, Table S4, ESI†). These results clearly provide a direct evidence that aryl or branched aldehydes cannot enter the cavity of pillar[5]arene while linear aldehydes can.

To further confirm this conclusion, an aromatic amine, *i.e.*, p-anisidine (**PA**), was introduced to the mixture of aldehydes, and the molar ratio of **PA** to other aldehydes was 1:3. In the absence of **DEP5A**, the decay of **G3** and the formation of imine $\mathbf{G3_i^{PA}}$ were found to be slow (Fig. 3a, Fig. S21-24, Table S5†). However, in the presence of **DEP5A** at a concentration of 100 mM, the decay of both **G1** and **G2** had obvious rate enhancement, and in sharp contrast, the proportion of **G3** stayed very stable and no corresponding imine $\mathbf{G3_i^{PA}}$ was detected (Fig. 3b, Fig. S25, Table S6†). More interestingly, further analysis of our NMR studies in Fig. 3b suggested a competitive reaction, aldol reaction, where **PA** acted as a catalyst and **DEP5A** as a co-catalyst.[48-50] Firstly, $\mathbf{G2_i^{PA}}$ formed immediately with the decay of **G2** within a period of 6 minutes. Subsequently, the $\mathbf{G2_i^{PA}}$ decreased with the decay of **G2**, and accordingly the detection by ^{1}H NMR indicated that a new aldehyde appeared (around δ_{ppm} 9.64), which came from the side aldol reaction where the representative chemical shift values of –CHO of aldol products lied in δ_{ppm} 9.71-9.62[51, 52] (Fig. S26-27, ESI†). Furthermore, the total amount of $\mathbf{G2_i^{PA}}$ and **G2** that participated in the observed aldol reaction was not equal to the total amount of **G2** as in Fig. 3b. This phenomenon can be ascribed to the formation of the uncontrolled intermediates (Scheme S1, ESI†).

For comparison, five-fold higher concentration of 1,4-diethoxybenzene monomer was used in the reaction system to replace **DEP5A** and thus to rule out the importance of supramolecular host **DEP5A** with a suitable cavity. As in Fig. 3c, Fig. S28, Table S7†, the reaction rate between reactant **G3** and the product $\mathbf{G3_i^{PA}}$ was obviously enhanced in the presence of high concentration of 1,4-diethoxybenzene, and the effects on the decay of **G1** and the formation of $\mathbf{G1_i^{PA}}$ were hardly observed. On one hand, these comparative studies of **DEP5A** and the 1,4-dimethoxybenzene monomer allow us to conclude that **DEP5A** acts as not only a shielder *via* host-guest inclusion complexation in the process of imine formation but also a specific catalyst that could promote the formation of a side aldol reaction. This catalytic property of **DEP5A** might originate from a strain-induced reactivity.[53] On the other hand, the lower reversibility of an aldol reaction, compared with imine formation, is a driving force for the rate enhancement of the decay of **G1** and **G2**.

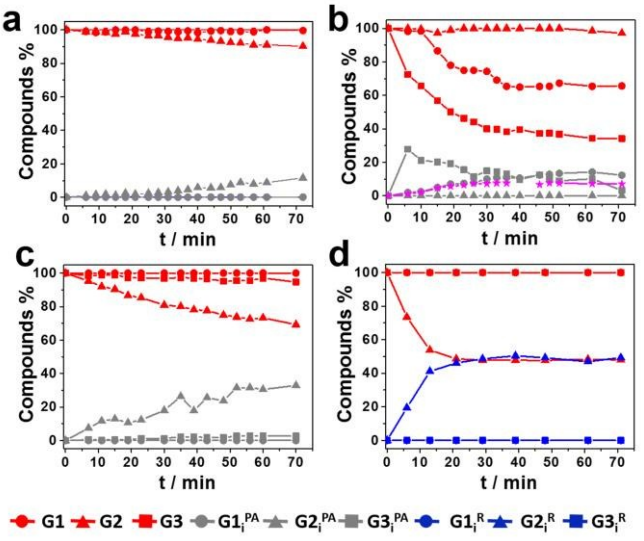

Fig. 3 Comparative studies of the constituent distribution of DCLs by 400 MHz at 25 °C, where each aldehyde (**G1**, **G2**, **G3**) of equal concentration (4 mM) in $CDCl_3$ was added a) in the absence of **DEP5A** or its monomer, or in the presence of b) **DEP5A** (25 equiv., ★ aldol product); c) the monomer (125 equiv.); d) **R** (3 equiv.). **PA** in a, b, and c is 4 mM (1.0 equiv.).

With the above information in hand, **R** is expected to play a powerful role in the segregation of **G1**, **G2** and **G3** in the imine formation because it can host non-hindered chemical reagents in its self-included version. Results of the constituent distribution of DCLs in the presence of **R** are discussed. When the molar ratio of the total three aldehydes to **R** was 3:1, it is **G3** that only reacts with the amino group (Fig. S29, Table S8, ESI†). To double-check hardly could **G2** react in this system, the molar ratio of mixed aldehydes to **R** was reset as 1:1, and surprisingly it was still **G3** that decayed and the corresponding imine $\mathbf{G3_i^R}$ was formed (Fig. 3d, Fig. S30, Table S9, ESI†). This could be explained by the fast exchange between the self-included and its free form of **R** in $CDCl_3$ that was extremely faster than imine formation, thus resulting in a stable self-included form of **R** in the DCLs, and only **G3** that could also be included in the cavity of pillarenes reacted. In addition, from Fig. 3d, we notice that the decay of **G3** and the formation of corresponding imine $\mathbf{G3_i^R}$ are not complete and the reaction reaches a steady state within 20 min, which are attributed to a direction between the reactive formyl group and **R** for host-guest recognition and the equilibrium of the reactants, the intermediate hemiaminal, and the imine product.

We hypothesized that our system could stabilize imines and hemiaminals for their direct detection by ESI-MS. So four kinds of aliphatic aldehydes, **G3**, benzenepropanal (**G4**), phenylacetaldehyde (**G5**), and 3,3-dimethylbutyraldehyde (**G6**) with different space effects were selected to react with **R** in a controlled method. Surprisingly, several groups of active imines and hemiaminals were detected as summarized in Table 1 and Fig. S31-S43, ESI†. Fig.4 demonstrates the reaction of **R** and **G5**. The exact mass of $[\mathbf{R}+H]^+$ is 963.5365, and the experimental mass is 964.0109. The systematic error is 0.4744. So the imine $[\mathbf{G5_i^R}+H]^+$ was corrected as 1065.6061 and the hemiaminal $[\mathbf{G5_h^R}+H]^+$ was corrected as 1083.6205, which are the same with the exact mass, 1065.5835 and 1083.5941, respectively. And an experimental mass of the hemiaminal $[\mathbf{G5_h^R}+H]^+$ was also observed as 1083.5828. Herein, two main reasons weigh in the stabilization of unstable imines and hemiaminals formed from aliphatic amine, **R**, and aldehydes. On one hand, the imine formation most likely happens within the confined cavity of **R** where the limited size of cavity excludes a molecule of water involved in the transition state (Scheme S2, ESI†), thus making the imines form slow and keep a comparative higher concentration of hemiaminals. On the other hand, the hydrophobic cavity of pillar[5]arene makes the reversible hydrolysis of imine difficult due to the hindrance of the entrance of water molecule. As a comparison, we also traced the imines and hemiaminals formed from aliphatic aldehydes and monomeric amine, the counterpart of **R** without pillarene cavity, showing no targeted signals of corresponding imines and hemiaminals at all by ESI-MS in the same conditions.

Table 1 Unstable imines and hemiaminals detected by ESI-MS.

		G3	G4	G5	G6
$[R+H]^+$	Theor.		963.5365		
	Exp.	964.0028	964.0017	964.0109	964.0028
	ΔR	0.4663	0.4652	0.4744	0.4663
$[Hemi.+H]^+$	Theor.	1063.6254	1097.6097	1083.5941	1063.6254
	Exp.	1064.1247	1098.1245	1084.0949	1064.1145
	Corr.	1063.6584	1097.6593	1083.6205	1063.6482
$[Imine+H]^+$	Theor.	1045.6148	1079.5991	1065.5835	1045.6148
	Exp.	1046.1129	1080.1009	1066.6060	1046.1107
	Corr.	1045.6466	1079.6357	1065.6061	1045.6444

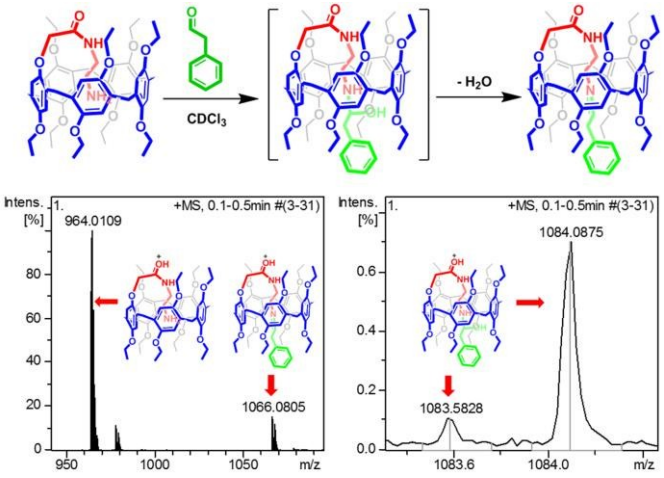

Fig. 4 ESI-MS of the reaction mixture of **R** and **G5**. The exact mass of $[\mathbf{R}+H]^+$ is 963.5365, and the experimental mass is 964.0109. The systematic error is 0.4744. The mass of imine, $[\mathbf{G5_i^R}+H]^+$, is corrected as 1065.6061. The mass of hemiaminal, $[\mathbf{G5_h^R}+H]^+$, is corrected as 1083.6205, and an experimental mass is observed as 1083.5828.

In conclusion, a functionalized pillar[5]arene analogue, *i.e.*, **R**, was designed and applied in the stabilization of aliphatic imines and hemiaminals in the solution states, as traced by LC-MS. Some model aldehydes were chosen, and the binding constants between aldehydes and **DEP5A** were measured, where **G3** was confirmed with a slight higher association (ca. 49 M^{-1}). The dynamic studies of the reactions between the aldehydes and **PA** in the presence of **DEP5A** or its monomer, 1,4-diethoxybenzene, comparatively concluded that the cavity of **DEP5A** plays a significant role. Finally, we investigated the reaction of a series of aldehydes and **R**, in which **G3** was the only one that could selectively react. We further expanded the reactions of **R** and other different aliphatic aldehydes with variable space effects, **G4**, **G5 and G6**, and the expected active imines and hemiaminals were observed by LC-ESI-MS. This work gives access to a promising application of functional synthetic macrocycles in rational design and molecule screening by both non-covalent and covalent interactions.

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Notes and references

1. T. Ogoshi, S. Kanai, S. Fujinami, T.-a. Yamagishi and Y. Nakamoto, *J. Am. Chem. Soc.*, 2008, **130**, 5022-5023.
2. H. Zhang, X. Ma, K. T. Nguyen and Y. Zhao, *ACS Nano*, 2013, **7**, 7853-7863.
3. W. Feng, M. Jin, K. Yang, Y. Pei and Z. Pei, *Chem. Commun.*, 2018, **54**, 13626-13640.
4. H. Zhang, Z. Liu and Y. Zhao, *Chem. Soc. Rev.*, 2018, **47**, 5491-5528.
5. N. Song and Y.-W. Yang, in *Pillararenes*, Ed. T. Ogoshi, The Royal Society of Chemistry, 2016, pp. 229-262.
6. J.-F. Chen, Q. Lin, Y.-M. Zhang, H. Yao and T.-B. Wei, *Chem. Commun.*, 2017, **53**, 13296-13311.
7. C. Sathiyajith, R. R. Shaikh, Q. Han, Y. Zhang, K. Meguellati and Y.-W. Yang, *Chem. Commun.*, 2017, **53**, 677-696.
8. W. Si, P. Xin, Z.-T. Li and J.-L. Hou, *Acc. Chem. Res.*, 2015, **48**, 1612-1619.
9. N. Song and Y.-W. Yang, *Chem. Soc. Rev.*, 2015, **44**, 3474-3504.
10. Y.-W. Yang, Y.-L. Sun and N. Song, *Acc. Chem. Res.*, 2014, **47**, 1950-1960.
11. N. Song, T. Kakuta, T.-a. Yamagishi, Y.-W. Yang and T. Ogoshi, *Chem*, 2018, **4**, 2029-2053.
12. T. Ogoshi, T.-a. Yamagishi and Y. Nakamoto, *Chem. Rev.*, 2016, **116**, 7937-8002.
13. X. Yan, B. Zheng and F. Huang, *Polym. Chem.*, 2013, **4**, 2395-2399.
14. Z. Zhang, C. Han, G. Yu and F. Huang, *Chem. Sci.*, 2012, **3**, 3026-3031.
15. P. J. Cragg and K. Sharma, *Chem. Soc. Rev.*, 2012, **41**, 597-607.
16. N. Song and Y.-W. Yang, *Sci. China Chem.*, 2014, **57**, 1185-1198.
17. N. L. Strutt, H. Zhang, S. T. Schneebeli and J. F. Stoddart, *Acc. Chem. Res.*, 2014, **47**, 2631-2642.
18. Y. Wang, G. Ping and C. Li, *Chem. Commun.*, 2016, **52**, 9858-9872.
19. M. Xue, Y. Yang, X. Chi, Z. Zhang and F. Huang, *Acc. Chem. Res.*, 2012, **45**, 1294-1308.
20. X. Li, Z. Li and Y.-W. Yang, *Adv. Mater.*, 2018, **30**, 1800177.
21. Z. Li, X. Li and Y.-W. Yang, *Small*, 2019, **15**, 1805509.
22. T. Ogoshi, R. Sueto, K. Yoshikoshi, Y. Sakata, S. Akine and T.-a. Yamagishi, *Angew. Chem. Int. Ed.*, 2015, **54**, 9849-9852.
23. X.-S. Du, C.-Y. Wang, Q. Jia, R. Deng, H.-S. Tian, H.-Y. Zhang, K. Meguellati and Y.-W. Yang, *Chem. Commun.*, 2017, **53**, 5326-5329.
24. M. Wang, X. Du, H. Tian, Q. Jia, R. Deng, Y. Cui, C. Wang and K. Meguellati, *Chin. Chem. Lett.*, 2019, **30**, 345-348.
25. Q. Jia, X. Du, C. Wang and K. Meguellati, *Chin. Chem. Lett.*, 2019, **30**, 721-724.
26. P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652-3711.
27. F. B. L. Cougnon and J. K. M. Sanders, *Acc. Chem. Res.*, 2012, **45**, 2211-2221.
28. A. Herrmann, *Chem. Soc. Rev.*, 2014, **43**, 1899-1933.
29. Q. Ji, R. C. Lirag and O. S. Miljanic, *Chem. Soc. Rev.*, 2014, **43**, 1873-1884.
30. Y. Jin, C. Yu, R. J. Denman and W. Zhang, *Chem. Soc. Rev.*, 2013, **42**, 6634-6654.
31. J. M. Lehn, *Chem. Eur. J.*, 1999, **5**, 2455-2463.
32. J.-M. Lehn and A. V. Eliseev, *Science*, 2001, **291**, 2331-2332.
33. M. Mondal and A. K. H. Hirsch, *Chem. Soc. Rev.*, 2015, **44**, 2455-2488.
34. E. Moulin, G. Cormos and N. Giuseppone, *Chem. Soc. Rev.*, 2012, **41**, 1031-1049.
35. N. Giri, M. G. Del Pópolo, G. Melaugh, R. L. Greenaway, K. Rätzke, T. Koschine, L. Pison, M. F. C. Gomes, A. I. Cooper and S. L. James, *Nature*, 2015, **527**, 216.
36. M. E. Belowich and J. F. Stoddart, *Chem. Soc. Rev.*, 2012, **41**, 2003-2024.
37. N. E. Hall and B. J. Smith, *J. Phy. Chem. A*, 1998, **102**, 4930-4938.
38. A. Heine, G. DeSantis, J. G. Luz, M. Mitchell, C.-H. Wong and I. A. Wilson, *Science*, 2001, **294**, 369-374.
39. T. Haneda, M. Kawano, T. Kawamichi and M. Fujita, *J. Am. Chem. Soc.*, 2008, **130**, 1578-1579.
40. T. Kawamichi, T. Haneda, M. Kawano and M. Fujita, *Nature*, 2009, **461**, 633.
41. W. Morris, C. J. Doonan and O. M. Yaghi, *Inorg. Chem.*, 2011, **50**, 6853-6855.
42. R. J. Hooley, T. Iwasawa and J. Rebek, *J. Am. Chem. Soc.*, 2007, **129**, 15330-15339.
43. T. Iwasawa, R. J. Hooley and J. Rebek, *Science*, 2007, **317**, 493-496.
44. L. Xu, S. Hua and S. Li, *Chem. Commun.*, 2013, **49**, 1542-1544.
45. Y. Han, G.-F. Huo, J. Sun, J. Xie, C.-G. Yan, Y. Zhao, X. Wu, C. Lin and L. Wang, *Sci. Rep.*, 2016, **6**, 28748.
46. J. Li, P. Nowak and S. Otto, *J. Am. Chem. Soc.*, 2013, **135**, 9222-9239.
47. X. Lou, H. Chen, X. Jia and C. Li, *Chin. J. Chem.*, 2015, **33**, 335-338.
48. V. T. Bhat, A. M. Caniard, T. Luksch, R. Brenk, D. J. Campopiano and M. F. Greaney, *Nat. Chem.*, 2010, **2**, 490.
49. A. Dirksen, S. Dirksen, T. M. Hackeng and P. E. Dawson, *J. Am. Chem. Soc.*, 2006, **128**, 15602-15603.
50. A. Dirksen, T. M. Hackeng and P. E. Dawson, *Angew. Chem. Int. Ed.*, 2006, **45**, 7581-7584.
51. K. Rohr and R. Mahrwald, *Org. Lett.*, 2012, **14**, 2180-2183.
52. S. Yamago, D. Machii and E. Nakamura, *J. Org. Chem.*, 1991, **56**, 2098-2106.
53. L. Ratjen, G. Vantomme and J. M. Lehn, *Chem. Eur. J.*, 2015, **21**, 10070-10081.

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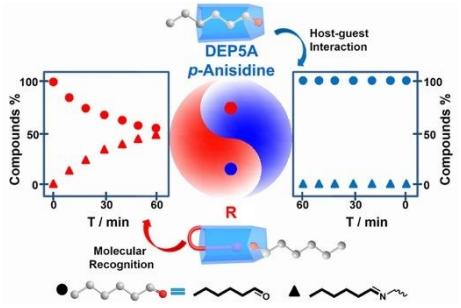

A self-included mono-amino substituted pillar[5]arene efficiently stabilizes the hemiaminal and imine formation from the reaction of aliphatic amines and aldehydes.