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Synthesis of novel chiral non-racemic substituted trianglimine and trianglamine macrocycles

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Abstract—The synthesis of novel 27- and 30-membered macrocycles of the trianglimine and trianglamine type is described, based on a [3+3] cyclocondensation between an enantiomerically pure 1,2-diamine and aromatic dicarboxaldehydes. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The development of supramolecular chemistry has been mainly driven by the availability of suitable macrocyclic receptors. Once a class of macrocyclic receptors with a unique shape, distinct architecture and set of functional groups becomes widely available from natural or synthetic sources, they start to inspire the imagination of supramolecular chemists to devise and synthesise novel sophisticated receptors, molecular machines and devices. Starting with Curtis' seminal synthesis of polyaza macrocycles,[1,2] continuing with Pederson's crown ethers and cryptands,[3,4] the cyclodextrins,[5] calix[*n*]arenes,[6–9] and curcubiturils,[10,11] any new class of macrocycle has led to a rapid development of innovative supramolecular chemistry and a considerable advancement of the subject. The main requirement for a macrocycle suitable to make an impact on supramolecular chemistry is its ease of synthesis in sufficiently large quantities combined with a unique molecular architecture and a particular set of functional groups that allow further elaboration into more sophisticated structures. Gawronski and co-workers[12] have recently introduced a new synthetic strategy for the synthesis of large poly-imine *meta*- and *para*-cyclophane type macrocycles using a [3+3] cyclocondensation strategy. Diastereomeric structures of this type of macrocycle have recently been reported by the group of Hodacova.[13] Other isolated examples of [3+3] cyclocondensation strategies have been reported.[14] Intrigued by this approach we started investigating the scope and limitation of the concept and would like to report in this short communication on significant extensions of Gawronski's basic scheme introducing novel unusual macrocycles. Due to their unique triangular shape we would like to suggest this new class of macrocycles be named trianglimines or trianglamines, respectively.

2. Results and discussion

In this communication we report on the extension of the [3+3] cyclocondensation concept to alkyl substituted dialdehydes **2**–**5**. These dialdehydes are challenging substrates for the [3+3] cyclocondensation, due to the decreased reactivity of the aldehyde functionalites for

Table 1. Yields of macrocycles **6**–**11** and **15**–**17** and MS data

Compound	LSIMS *m*/*z*	Isolated yield (%)	Compound	LSIMS *m*/*z*	Isolated yield (%)
6[15]	708.3	97	**11**[16]	692.3	89
7	667.2	69	all-(*R*)-**15**	932.4	17
8	667.3	75	all-(*S*)-**15**	932.4	19
9	748.4	90	**16**	932.3	Crude yield: 20
10	692.3	94	**17**	944.4	92

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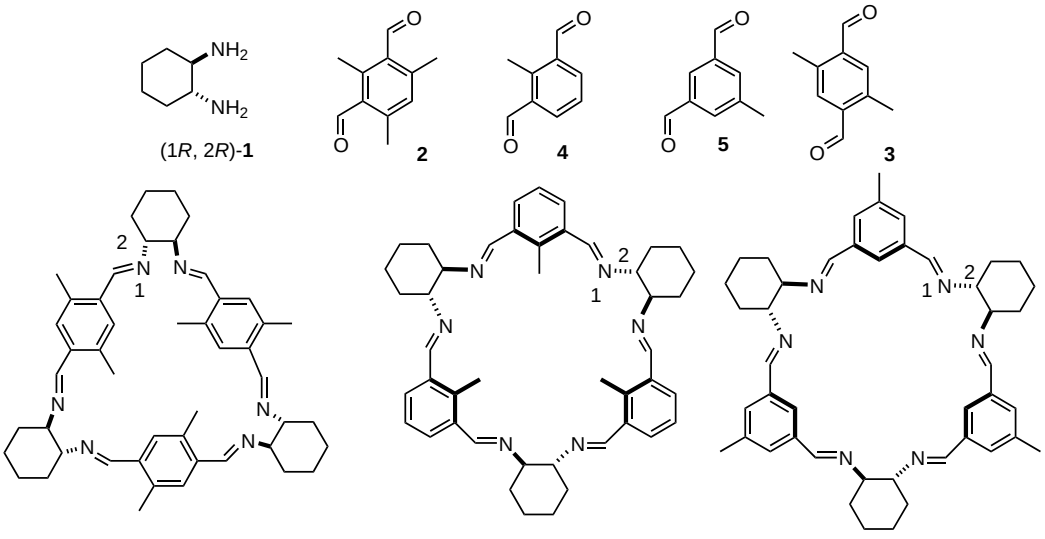


(1*R*, 2*R*)-**1** **2** **4** **5** **3**

(2*R*, 3*R*, 12*R*, 13*R*, 22*R*, 23*R*)-**6** (2*R*, 3*R*, 11*R*, 12*R*, 20*R*, 21*R*)-**7** (2*R*, 3*R*, 11*R*, 12*R*, 20*R*, 21*R*)-**8**

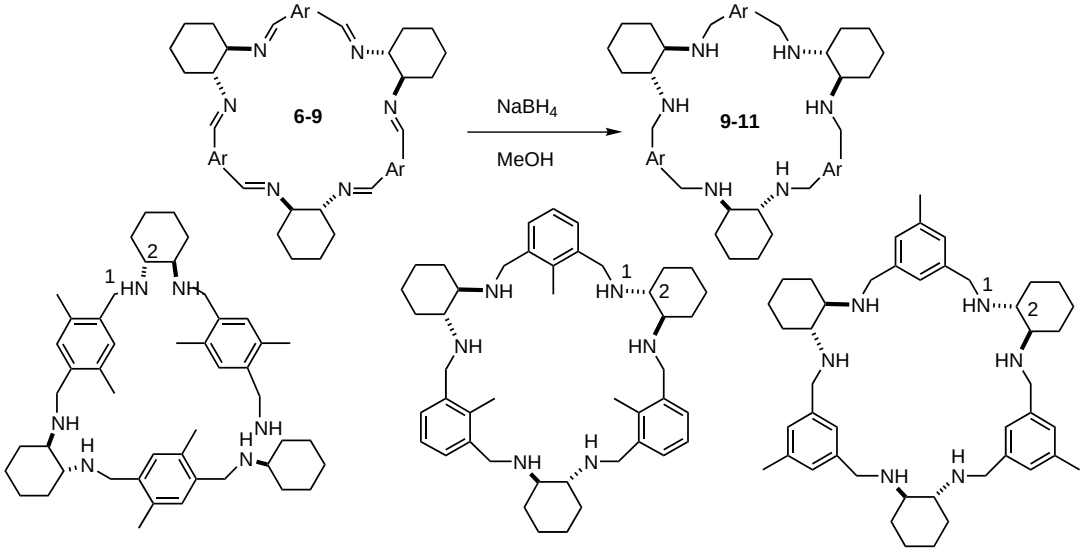
both electronic and steric reasons. Additionally, the substituents on the dialdehyde moiety would allow formation of various conformers of the resulting macrocycle.

Cyclocondensation between (1*R*,2*R*)-**1** and methyl substituted dialdehydes **3**–**5** gave, under standard conditions at 0.05 M concentration in dichloromethane, the macrocyclic trianglimines **6**–**8**.

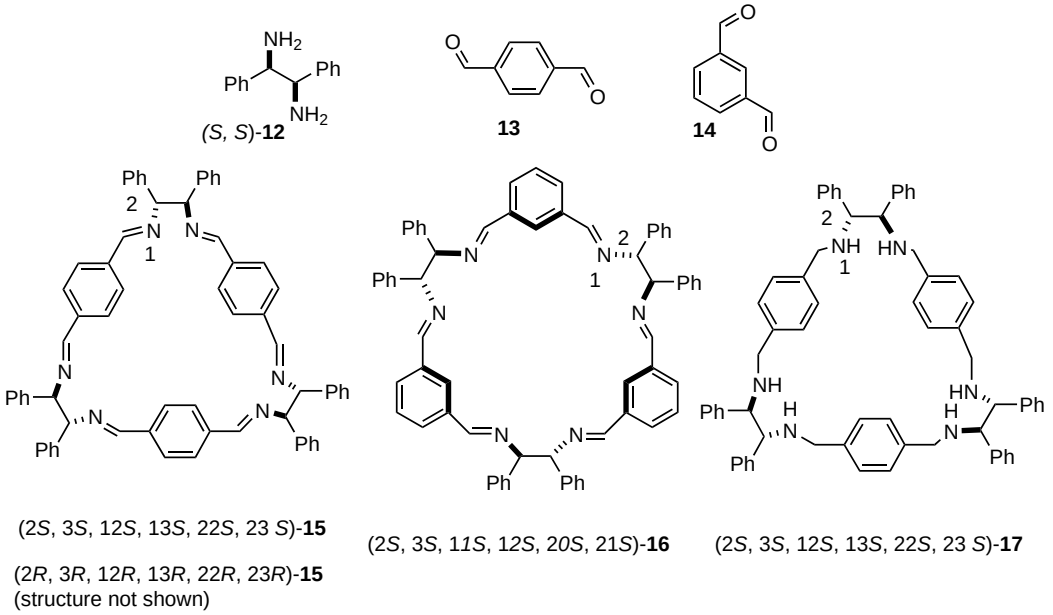
Trianglimine **6**[15] was formed in quantitative yield, whereas compounds **7** and **8** were formed in very good yield along with some 'dimeric structures' (according to the crude MS at m/z 462) and some unidentified by-products (for yields see Table 1). They could be obtained in analytically pure form after recrystallisation from toluene or ethyl acetate. Dialdehyde **2** failed to give any macrocyclic product. All trianglimines display the predicted spectroscopic features, most importantly one set of NMR signals due to their inherent C_3 or D_3 symmetry, respectively, for the preferred conformation adopted in solution. They all show the expected molecular ion in the LSIMS mass spectra. There was no evidence obtained on alternative conformers devoid of any symmetry element.

Reduction of the trianglimines **6**–**8** with $NaBH_4$ in MeOH gave the trianglamines **9**–**11** in excellent yields (see Table 1). Due to their additional alkyl groups the novel macrocycles are reasonably soluble in chloroform. Again the macrocycles isolated show NMR spectra that are in agreement with a perfect C_3 symmetric conformation for **10** and **11**[16] and a D_3 symmetric conformation for **9**. The LSIMS mass spectra show the expected molecular ions exclusively.

Next we turned our attention to the condensation between an open chain 1,2-diamine and aromatic



(2*R*, 3*R*, 12*R*, 13*R*, 22*R*, 23*R*)-**9** (2*R*, 3*R*, 11*R*, 12*R*, 20*R*, 21*R*)-**10** (2*R*, 3*R*, 11*R*, 12*R*, 20*R*, 21*R*)-**11**



dialdehydes **13** and **14**. (*R*,*R*)- and (*S*,*S*)-**12** seem to be ideal candidates since both enantiomers are commercially available. The cyclocondensation between (*R*,*R*)-**12** and (*S*,*S*)-**12** and terephthalaldehyde **13** yielded the two enantiomeric macrocycles **15** in moderate yields along with some linear oligomers as judged by a crude LSIMS-MS spectrum.

Reaction of (*S*,*S*)-**12** and isophthalaldehyde **14** gave macrocycle **16**, which we failed to obtain analytically pure.

After repeated column chromatography macrocycles **15** could be isolated in pure form. Similar to Gawronski's trianglimines the 'trimeric' cyclisation precursor (three diamines+three dicarbonyls) seems to adopt a minimum energy conformation, in which cyclisation competes with linear extension.[13]

Due to the increased conformational flexibility of the alicyclic diamine (*S*,*S*)-**12**, the yields for the macrocycles **15** and **16** are reduced in comparison to those obtained with the cyclic conformationally more restricted diamine **1**. However, on standing in solution the trianglimine **15** decomposes after 2 days in $CDCl_3$ to give linear oligomeric products, suggesting that the trianglimine is the kinetic product of the reaction. Reduction of **15** with $NaBH_4$ gave trianglimine **17** allowing the synthesis of a stable derivative.

3. Conclusion

In conclusion we have shown that the [3+3] cyclocondensation strategy can be applied to a range of substrates including substituted dialdehydes and open chain enantiomerically pure 1,2-diamines. In this outstanding reaction six new carbon nitrogen bonds are formed. All compounds synthesised are highly useful intermediates and building blocks for macrocyclic chemistry and will turn out to be valuable receptor molecules in supramolecular chemistry.

Acknowledgements

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References

1. Curtis, N. F. *J. Chem. Soc.* **1960**, 4409.
2. Curtis, N. F. *J. Chem. Soc.* **1964**, 2645.
3. *Cation Binding by Macrocycles—Complexation of Cationic Species by Crown Ethers*; Inoue, I.; Gokel, G. W., Eds., Marcel Dekker Publisher: Basel, New York, 1990
4. Pederson, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.
5. For cyclodextrins see special edition of Chemical Reviews, 1998, *98*, Issue 5.
6. Gutsche, C. D. In *Calixarenes*; Stoddart, J. F., Ed. Monographs in Supramolecular Chemistry. Royal Society of Chemistry: Cambridge, 1989.
7. Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed. Monographs in Supramolecular Chemistry. Royal Society of Chemistry: Cambridge, 1998.
8. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.
9. Danil de Namor, A. F.; Cleverley, R. M.; Zapata-Ormachea, M. L. *Chem. Rev.* **1998**, *98*, 2495–2525.
10. Kim, J.; Jung, I. S.; Kim, S. Y.; Lee, E.; Kang, J. K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540–541.
11. Kim, S. Y.; Jung, I. S.; Lee, E.; Kim, J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2119–2121.

12. Gawronski, J.; Kolbon, H.; Kwit, M.; Katrusiak, A. *J. Org. Chem.* **2000**, *65*, 5768–5773.
13. Chadim, M.; Budesinsky, M.; Hodacova, J.; Zavada, J.; Junk, P. C. *Tetrahedron: Asymmetry* **2001**, *12*, 127–133.
14. (a) Korupoju, S. R.; Zacharias, P. S. *Chem. Commun.* **1998**, 1267–1268; (b) Korupoju, S. R.; Mangayarkarasi, N.; Ameerunisha, S.; Valente, E. J.; Zacharias, P. S. *J. Chem. Soc., Dalton Trans.* **2000**, *65*, 2845–2852.
15. Analytical data for compound **6**. Mp over 200°C; $[\alpha]_D^{25}$ +221 ($CHCl_3$, $c=0.1$); IR ν_{max} (Nujol)/cm^{-1}: 1636 (C=N), 1606–1463 (C_{Ar}=C_{Ar}), 815; ^1H NMR (500 MHz; $CDCl_3$) δ_H 8.43 (6H, s, N=CH), 7.51 (6H, s, Ar), 3.41 (6H, m, CHN=C), 2.51–2.30 (m, 12H, CH_2), 2.31 (18H, s, Me), 1.49–1.86 (24H, m, CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 159.3, 135.9, 135.3, 128.7, 75.1, 33.2 24.9, 18.5; CHN calcd: C, 80.0; H, 8.39; N, 11.66; found: C, 79.6; H, 8.21; N, 11.2%; MS (LSIMS): $C_{48}H_{60}N_6$ (m/z 721.3, M+H).
16. Analytical data for compound **11**. Mp over 200°C; $[\alpha]_D^{25}$ −192 ($CHCl_3$, $c=0.1$); IR ν_{max} (Nujol)/cm^{-1}: 3420 (br, NH), 1604, 1463, 815; ^1H NMR (500 MHz; $CDCl_3$) δ_H 7.11 (3H, s, CH), 6.97 (6H, s, CH), 3.79 (6H, d, $J=$ 13.1 Hz, CH_AH_BN), 3.56 (6H, d, $J=13.1$ Hz, CH_AH_BN), 2.29 (9H, s, Me), 2.13 (6H, s, br, exchanges with D_2O, NH), 2.03 (6H, m, CHN), 1.20–1.88 (24H, m, CH_2); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 141.8, 138.2, 127.9, 124.9, 61.4, 51.4, 32.2, 25.7, 21.7; CHN calcd: C, 78.2; H, 9.63; N, 12.16%; found: C, 77.6; H, 9.81; N, 11.91%; MS (LSIMS): $C_{45}H_{66}N_6$ (m/z 691.2, M+H).