An experimental re-investigation of the role of aromatic–aromatic interactions in a templated synthesis of a macrocyclic pseudopeptide

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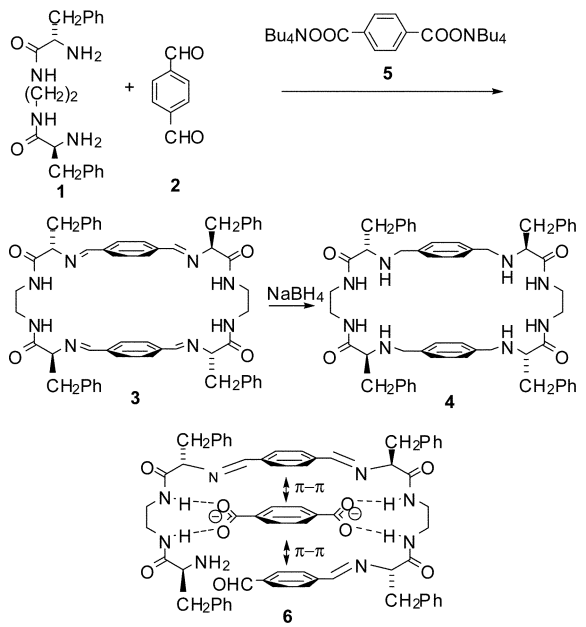
The experimental re-investigation of a reported synthesis of a macrocyclic pseudopeptide promoted by bis(tetrabutylammonium)terephthalate allowed us to elucidate the nature of the non-bonding interactions between the reagents and the template; while the involvement of aromatic–aromatic interactions could be ruled out, the relevance of the role of the carboxylate ion was confirmed.

It was recently reported[1] that the macrocyclization of the bisphenylalanine derivative **1** with dialdehyde **2** in MeOH (Scheme 1) afforded the desired macrocycle **3** in good yield (60–65% as determined on the more easily isolated reduction product **4**)[2] only if the reaction occurred in the presence of the bis(tetrabutylammonium) salt of terephthalic acid **5** acting as a template. In its absence, only linear oligomeric products were formed.



Scheme 1 Templated synthesis of macrocyclic pseudopeptide **4**.

Strong evidence, both experimental (mass spectrometry, NMR and CD spectroscopy) and theoretical (Monte Carlo conformational analysis), was collected, pointing to an active role of the template, that was able to promote the macrocyclization through a combination of favourable non-bonding interactions. As shown in structure **6**, these were believed to involve hydrogen-bond formation between the amide hydrogens of **1** and the carboxylate anions of **5**, and an attractive aromatic–aromatic π-stacking interaction between the aromatic ring of the template and those of the reagents.[1]

The putative involvement of a π-stacking interaction in this macrocyclization reaction attracted our attention because, on the basis of our experience in the field,[3] the observation of aromatic–aromatic non-bonding interactions[4] in solution and for a conformationally non-restricted system,[5] is extremely rare.[6,7] Therefore, we decided to assess the actual importance of aromatic interactions in this case by an experimental re-investigation.

We first reasoned that the validity of the π-stacking interaction hypothesis could be readily tested by replacing template **5** with its tetrafluoro analog **7** (Fig. 1). On the basis of others[5] and our own work,[3c] this modification was expected to result in an increase in the macrocyclization yield because of an attractive interaction between aromatic rings of opposite charge distribution.[4,5,8] It must be noted that the polar reaction solvent MeOH, which should favour the hydrophobic component of the aromatic–aromatic interaction,[4,5] was expected to maximize this phenomenon.

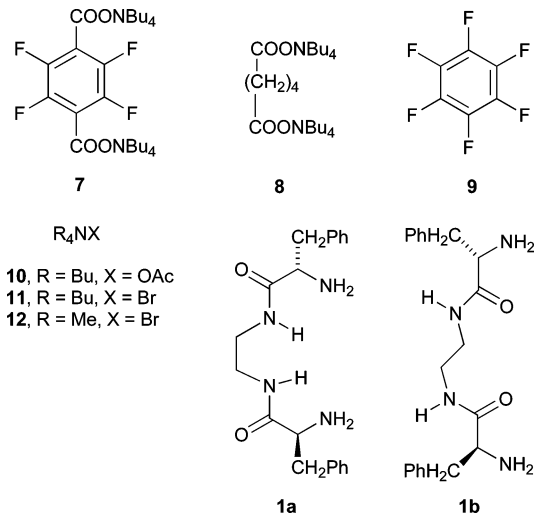


Fig. 1 Structures of additives **7–12** and of conformations **1a** and **1b**.

However, when the macrocyclization was carried out in the presence of **7** under the reported conditions,[1] no improvement in the yield was observed, and the reactions carried out with **5** or **7** afforded **4** in identical isolated yield (58%). The macrocyclization yield remained almost the same (56%) also when the reaction was performed in the presence of bis(tetrabutylammonium) adipate **8**, a template that obviously cannot benefit from any π–π interaction. On the other hand, the use of hexafluorobenzene **9** as a template

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potentially allowing π-stacking interactions but not hydrogen-bonds,[9] did not lead to the isolation of any macrocyclic product.

These experiments strongly suggested that the involvement of an aromatic–aromatic interaction between the template and the substrate in the macrocyclization could be ruled out; on the other hand the formation of hydrogen-bonds between the amide hydrogens and the carboxylate ions could indeed be an important factor by which the template was exerting its effect, as originally proposed.[1]

To further investigate the importance of the role of the carboxylate group in favoring the macrocyclization, the reaction was carried out in the presence of tetrabutylammonium acetate **10** as an additive. We were pleased to find that the use of 1 mol equiv. of **10** promoted a high-yielding macrocyclization, allowing the isolation of **4** in 86% yield. This result seemed to indicate that it is not necessary for the template to carry two carboxylate functionalities as in **5**, **7**, and **8**. Rather, the presence of a single carboxylate group in the additive appears to be sufficient to induce enough conformational pre-organization in the macrocycle precursor to efficiently undergo ring closure.

To conclusively establish the central role of the carboxylate anion, the macrocyclization reaction was carried out in the presence of tetrabutylammonium bromide **11**. We were surprised to find that also the use of 1 mol equiv. of **11** promoted the reaction, although in only 20% isolated yield. To explain this observation, one can make the hypothesis that the ammonium cation could favour the cyclization acting as a template by an attractive interaction with the lone pairs of the amide oxygens of the bisphenylalanine moieties of the macrocycle precursor.[10,11] The weaker nature of this interaction with respect to that between the carboxylate ion and the amide hydrogens,[13] can be considered in a qualitative agreement with the difference in chemical yield observed in the reactions promoted by **10** and **11**.

To further check the validity of the hypothesis of an involvement of the ammonium cation in the macrocyclization, the reaction was also performed in the presence of tetramethylammonium bromide **12**, with the expectation of observing an increase in the templating effect (and, as a consequence, in the macrocyclization yield) because this cation, smaller than **11**, should be co-ordinated more easily by the macrocyclic precursor. However, in the presence of **12** the macrocyclization yield dropped to 11%. This result clearly pointed to a very minor contribution, if any, of the ammonium cation as significant templating additive.

In conclusion, the experimental re-investigation of this macrocyclic pseudopeptide synthesis allowed us to rule out the involvement of aromatic–aromatic interactions, while confirming the dominant role of the carboxylate ion. From a more general standpoint, these results contribute to show how difficult it is to observe an aromatic–aromatic interaction in solution, whose existence in a conformationally non-restricted system is frequently claimed[4,6] but seldom firmly demonstrated.[5]

References

1 M. Bru, I. Alfonso, M. I. Burguete and S. V. Luis, *Angew. Chem., Int. Ed.*, 2006, **45**, 6155–6159. We are indebted to Dr I. Alfonso for providing us with useful information on the chromatographic purification of macrocycle **4**.

2 It seems reasonable that the irreversible imine reduction step should not affect the distribution of the products of the macrocyclization reaction or the yield of the latter in adduct **3**. ^{1}H-NMR analysis of the crude reaction mixture before reduction showed the expected signals for adduct **3** (see ref. 1), and no signals imputable to the presence of unreacted aldehyde **2** or to the formation of detectable amounts of unstable emiaminal products.

3 (*a*) R. Annunziata, M. Cinquini, F. Cozzi, T. Dwyer and J. S. Siegel, *J. Am. Chem. Soc.*, 1992, **114**, 5729–5733; (*b*) R. Annunziata, M. Cinquini, F. Cozzi and J. S. Siegel, *J. Am. Chem. Soc.*, 1993, **115**, 3530–3531; (*c*) R. Annunziata, M. Cinquini, F. Cozzi, F. Ponzini and J. S. Siegel, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1019–1020; (*d*) F. Cozzi, R. Annunziata, M. Benaglia, M. Cinquini, L. Raimondi, K. K. Baldridge and J. S. Siegel, *Org. Biomol. Chem.*, 2003, **1**, 157–162.

4 For a review on aromatic–aromatic interactions see: E. A. Meyer, R. K. Castellano and F. Diederich, *Angew. Chem., Int. Ed.*, 2003, **42**, 1210–1250.

5 On the contrary, the observation of aromatic–aromatic interactions in conformationally restricted systems is well precedented. For a recent comprehensive article on the subject including an exhaustive list of references see: S. L. Cockroft, J. Perkins, C. Zonta, H. Adams, S. E. Spey, C. M. R. Low, J. G. Vinter, K. R. Lawson, C. J. Urch and C. A. Hunter, *Org. Biomol. Chem.*, 2007, **5**, 1062–1080.

6 To the best of our knowledge there is a single observation of a π-stacking aromatic–aromatic interaction occurring in solution for a confomationally unrestricted molecule: Y. El-Azizi, A. Schmitzer and S. K. Collins, *Angew. Chem., Int. Ed.*, 2006, **45**, 968–973.

7 On the contrary, the existence of parallel-stacked arrangements of aromatic rings in the solid state is very well precedented. For a recent example including a list of relevant references to earlier work see: S. Bacchi, M. Benaglia, F. Cozzi, F. Demartin, G. Filippini, T. Pilati and A. Gavezzotti, *Chem.–Eur. J.*, 2006, **12**, 3538–3546; and references cited therein.

8 For a review on aromatic–perfluoroaromatic interactions see: J. H. Williams, *Acc. Chem. Res.*, 1993, **26**, 593–598.

9 J. D. Dunitz and R. Taylor, *Chem.–Eur. J.*, 1997, **3**, 89–98. In this paper it is stated that: "organofluorine almost never accepts hydrogen-bonds".

10 The possibility exists that the ammonium ion could have a favourable interaction also with the π-electrons of the aromatic ring of the dialdehyde; for a recent review on cation–π interactions see: N. Zacharias and D. A. Dougherty, *Trends Pharmacol. Sci.*, 2002, **23**, 281–287. However, the large dimension of the tetrabutylammonium cation and the electron poor nature of the aromatic rings involved suggest that this cation–π interaction, if present, should be extremely weak and its effect in promoting the macrocyclization, if any, negligible.

11 Calculations showed that a conformation allowing the carbonyl oxygens–ammonium cation interaction was indeed accessible to compound **1**. First, systematic pseudo-Monte Carlo conformational analysis[12] showed that conformation **1a** (favouring hydrogen-bonding with a carboxylate anion) and **1b** (favouring the lone pair–cation interaction) were almost iso-energetic, and 1 kcal mol^{-1} higher in energy with respect to the global minimum. Second, stochastic dynamics simulations[12] showed that **1a** and **1b** were easily accessible in the presence of an acetate ion and of a tetramethylammonium cation, respectively. Starting from the global minimum conformation of the systematic pseudo-Monte Carlo conformational analysis, the adoption of a conformation suitable for interaction with the acetate and tetramethylammonium ions was complete in 5 and 10 ps, respectively.

12 MacroModel 7.1 package (Schroedinger, LLC, 2001): F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440–467. All calculations were performed in vacuum with MM2 force field as implemented in the MacroModel package.

13 The hydrogen-bond between the amide group and the carboxylate anion should be very strong. For a review discussing the relative energies of hydrogen-bonds see: G. R. Desiraju, *Acc. Chem. Res.*, 2002, **35**, 565–573.

