

Bifunctional receptor triad for efficient recognition of mono- and dicarboxylic acids†

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An equimolar mixture of two conformers of *Cinchona* alkaloid based triads containing an aromatic diimide spacer is transformed with high efficiency into the *syn* conformer in the presence of dicarboxylic acids or into the *anti* conformer in the presence of monocarboxylic acids. The recognition process is readily observed by ^1H NMR spectroscopy.

Studies of various supramolecular systems designed as receptors and sensors, switches and molecular machines have recently received much attention and a number of important achievements in this area have been documented.¹ The majority of the examples of receptors, sensors and switches can be classified as *monofunctional*, since they recognize a substrate or narrow class of similar structures with the same type of functionality. A more attractive and less explored approach involves *polyfunctional* systems, where the host molecule recognizes multiple functionality and produces an analytical signal acting in two different modes.²

Good platforms for construction of bifunctional receptors or switches are molecular triads A–B–A.³ A number of triads contain an aromatic diimide spacer (B) which restricts rotation around the C–N_{imide} bond and may lead to atropisomerism. Two distinct conformers of the triad—*syn* and *anti*, illustrated in Fig. 1, with approximately the same steric energy—are present in solution as an equimolar conformer mixture. *syn* and *anti* conformers have different geometry (*syn* is more compact) and consequently differ in recognition ability.⁴

Shimizu demonstrated that triads with a 1,4,5,8-naphthalenetetracarboxydiimide spacer can be converted to either *syn* or *anti* conformers by heating⁵ or a complexation–decomplexation strategy.⁶ These and other studies revealed that *syn* conformers are more readily obtained in solution whereas *anti* conformers occur more frequently in the solid state.

We assume that if unit A contains an effective binding site, switching between conformers can be affected by the recognition process using either mono- or bifunctional guest molecules. As promising binding part B of triads we choose *Cinchona* alkaloids since they contain the strongly basic quinuclidine nitrogen atom, responsible for their catalytic and resolving properties.⁷ Herein we report that molecular triads **1** and **2** which contain the (8*R*,9*R*)-9-*epi*-dihydrocinchoninyl moiety and either a 1,2,4,5-benzenetetracarboxydiimide or a 1,4,5,8-naphthalenetetracarboxydiimide spacer are efficient bifunctional receptors. In solution they quantitatively change their conformation to either *syn* or *anti* during the recognition process.

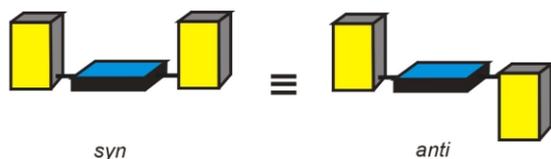
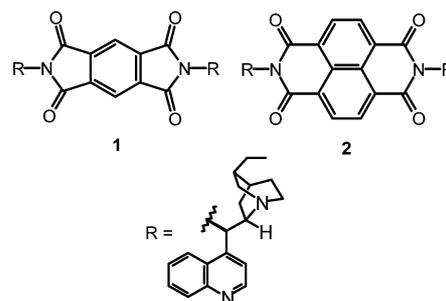


Fig. 1 *syn* and *anti* conformers of triad A–B–A.



^1H NMR spectra of **1** and **2** in deuterated solvents (chloroform–methanol 2 : 1) show that both *syn* and *anti* conformers are present in solution in equal amounts. Signals of pyromellitic protons of both conformers of **1** occur as singlets whereas those of the protons of the 1,4,5,8-naphthalenetetracarboxydiimide core in triad **2** are two singlets for the *anti* conformer and two doublets for the *syn* conformer.⁸

Addition of 2–3 equivalents of trifluoroacetic or benzoic acid to the solution of **2** causes quantitative conversion of the conformer mixture to the *anti* conformer (see Fig. 2). The strength of the acid is important for the efficiency of the recognition process and guests of $\text{p}K_{\text{a}} > 4.2$ are insufficient for the quantitative conformational conversion. For example, 3 equiv. of 4-*tert*-butylbenzoic or (*R*)-mandelic acid induced formation of 63% or 82% *anti* conformers, respectively.

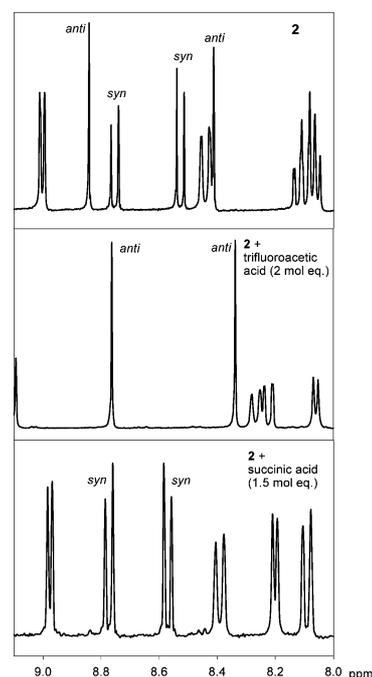


Fig. 2 Imide region ^1H NMR spectra (remaining signals are due to the quinoline protons).

† Electronic supplementary information (ESI) available: experimental details, spectrometric titration results, ESMS spectrum of the complex of **2** with (*R,R*)-tartaric acid. See <http://www.rsc.org/suppdata/cc/b3/b302003g/>

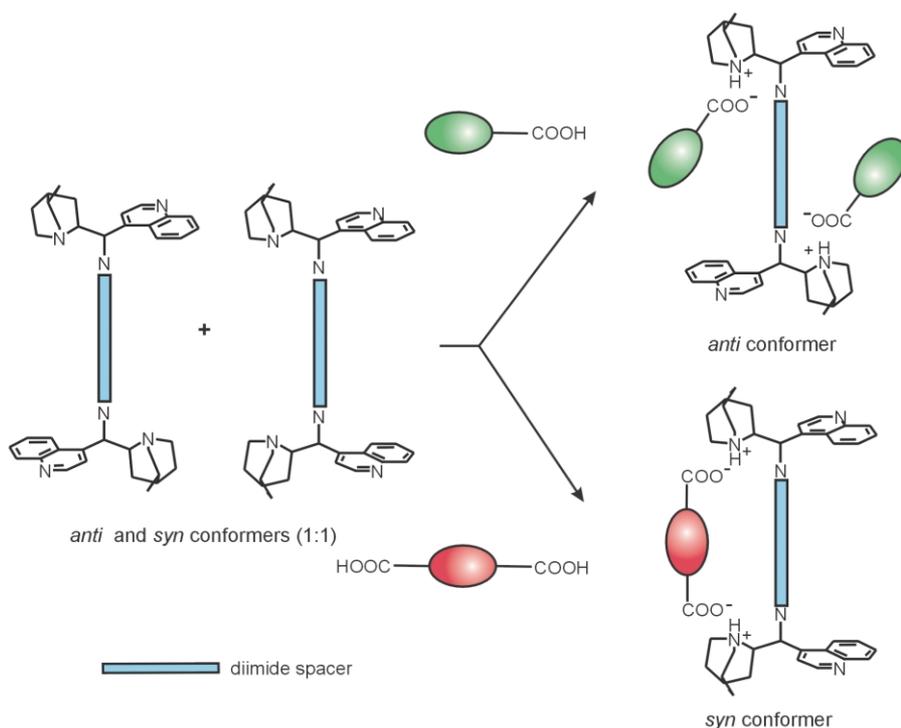


Fig. 3 Association modes of triads **1** and **2** with acids. Structures obtained by semiempirical (AM1) computations.

Table 1 Recognition of acids by triad **2**^a

| Guest (mol equiv.) | Signals of the imide protons | Conformer distribution (%) <i>syn</i> : <i>anti</i> |
|---------------------------------------|--|--|
| No guest | 8.84 (s), 8.52 (d) 8.75 (d), 8.41 (s) | 50 : 50 |
| Trifluoroacetic acid ^b (2) | 8.77 (s), 8.34 (s) | 0 : 100 |
| Benzoic acid (3) | 8.58 (s), 8.13 (s) | 0 : 100 |
| 4- <i>tert</i> -Butylbenzoic acid (3) | 8.77 (s), 8.74 (d) 8.53 (d), 8.40 (s) | 37 : 63 |
| (<i>R</i>)-Mandelic acid (3) | 8.78 (d), 8.68 (s) 8.57 (d), 8.27 (s) | 18 : 82 |
| Succinic acid (1) | 8.78 (d), 8.58 (d) | 100 : 0 |
| Adipic acid (1) | 8.84 (s), 8.75 (d) 8.55 (d), 8.44 (s) | 75 : 25 |
| (<i>S</i>)-Malic acid (1) | 8.79 (d), 8.58 (d) | 100 : 0 |
| (<i>R,R</i>)-Tartaric acid (1) | 8.71 (d), 8.46 (d) | 100 : 0 |
| (<i>S,S</i>)-Tartaric acid (1) | 8.78 (d), 8.55 (d) | 100 : 0 |
| <i>meso</i> -Tartaric acid (1) | 8.77 (d), 8.56 (d) | 100 : 0 |
| Dimethyl (<i>R,R</i>)-tartrate (3) | 8.83 (s), 8.75 (d) 8.54 (d), 8.44 (s) | 50 : 50 |

^a All measurements in CDCl₃-CD₃OD (2 : 1) solution. ^b In CDCl₃.

When four-carbon dicarboxylic acids, such as succinic, malic or tartaric acids, were used, just one molar equivalent of the diacid was sufficient to quantitatively produce the *syn* conformer of triad **2**. Adipic acid generated *syn* conformer only when used in excess (3 mol equiv.). The results are summarized in Table 1 and Fig. 2. In a competition experiment with benzoic (3 mol equiv.) and succinic acids (1.5 mol equiv.) a ratio *syn* : *anti* = 71 : 29 was obtained, indicating a higher affinity of dicarboxylic acids to receptor **2**. With dimethyl tartrate as the guest no change in conformer distribution was observed.

A mechanism of this conformation-switching recognition process, shown in Fig. 3, assumes protonation of the quinuclidine nitrogen atoms by the acid.

The stoichiometry of the complexes was determined by NMR titration in CDCl₃-CD₃OD (2 : 1) solution, to give triad **2** : acid ratio 1 : 2 with benzoic acid and 1 : 1 ratio with succinic acid. Additionally, a 1 : 1 ratio of **2** to (*R,R*)-tartaric acid in the complex was determined by ESI MS (C₅₆H₅₇O₁₀N₆]¹⁺ *M* = 973).

Further work in the direction of chiral recognition with triads **1** and **2** is in progress.

Notes and references

‡ Triad **1** is effective in the recognition process, however signals of the protons of the pyromellitic core are partially eclipsed by signals of the quinuclidine protons. In addition the signals are broad due to a low rotational barrier (22.8 kcal mol⁻¹ for **1** vs. 28.6 kcal mol⁻¹ for triad **2**) around the C-N bond. See supplementary information for details.

- S. H. Gellman (ed.), *Chem. Rev.*, 1997, **97**, 1231–1734; J. L. Atwood, J. M. Lehn, J. E. D. Davies, D. D. MacNicol, F. Vogtle (eds.), *Comprehensive Supramolecular Chemistry*, vol. 1–11, Pergamon Press, 1996; J. M. Lehn, *Supramolecular Chemistry. Concepts and Perspectives*, Wiley-VCH, Weinheim, 1995.
- Selected examples: L. Fabbrizzi, M. Licchelli, F. Mancin, M. Pizzeghello, G. Rabaoli, A. Taglietti, P. Tecilla and U. Tonellato, *Chem. Eur. J.*, 2002, **8**, 94; T. Gunnlaugsson, A. P. Davis, J. E. O'Brien and M. Glynn, *Org. Lett.*, 2002, **4**, 2449; Y. Aoyama, A. Yamagishi, M. Asagawa, H. Toi and H. Ogoshi, *J. Org. Chem.*, 1988, **110**, 4076.
- Recent review: J. Gawronski and K. Kacprzak, *Chirality*, 2002, **4**, 689.
- C. Degenhardt, D. B. Shortell, R. D. Adams and K. D. Shimizu, *Chem. Commun.*, 2000, 929; S. Kohmoto, K. Sakayori, K. Kishikawa and M. Yamamoto, *J. Chem. Soc., Perkin Trans. 2*, 1999, 833.
- D. S. Choi, Y. S. Chong, D. Whitehead and K. D. Shimizu, *Org. Lett.*, 2001, **3**, 3757.
- Y. S. Chong, M. D. Smith and K. D. Shimizu, *J. Am. Chem. Soc.*, 2001, **123**, 7463.
- K. Kacprzak and J. Gawronski, *Synthesis*, 2001, 961.
- J. Gawronski, K. Gawronska and K. Kacprzak, *Chirality*, 2001, **13**, 322.