Pergamon

Tetrahedron Letters 43 (2002) 8103–8106

TETRAHEDRON LETTERS

Recognition and binding of paraquat dichloride by cyclodextrin/calix[6]pyrrole binary host systems

Grazia Cafeo,[a] Claudia Gargiulli,[a] Giuseppe Gattuso,[a,*] Franz H. Kohnke,[a] Anna Notti,[a] Salvatore Occhipinti,[b] Sebastiano Pappalardo[b] and Melchiorre F. Parisi[a]

[a]*Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, I-98166 Messina, Italy*
[b]*Dipartimento di Scienze Chimiche, Università di Catania, Viale A. Doria 6, I-95125 Catania, Italy*

Received 10 May 2002; accepted 9 September 2002

Abstract—The synergic effect of paired anion and cation receptors in the recognition of organic salts is demonstrated by the combined action of acylated cyclodextrins and calix[6]pyrrole in the solubilisation and complexation of paraquat dichloride in organic solvents, and its extraction from water solution into dichloromethane. © 2002 Elsevier Science Ltd. All rights reserved.

Recognition and binding of salt species by neutral receptors is generally plagued by adverse ion-pairing effects which tend to compete with the mutual host–guest affinity.[1] Heteroditopic receptors have been devised to circumvent these unfavourable conditions.[2] However, the syntheses of such receptors are generally laborious, as they require careful design and multistep procedures. As an alternative, ion-pair extraction and transport of inorganic salts have been accomplished by the use of mixtures of synthetically more accessible anion and cation receptors.[3] In this context, we have recently demonstrated that strong enhancements in the complexation of ion-paired organic salts in non-polar media can be achieved by carefully chosen 'binary host systems'.[4]

In view of the high toxicity of paraquat dichloride **1** and its widespread use as a herbicide,[5] the development of binary host systems specialised in the selective extraction (and removal) of paraquat dichloride from aqueous into organic media is highly desirable. Unlike native cyclodextrins (CDs),[6] which preferably bind uncharged organic species in aqueous solution,[7] some chemically modified CDs behave as receptors for organic ions in non-aqueous media.[8] Specifically, *O*-acetylated CDs (namely, per-2,6-*O*-dialkyl-3-*O*-acetyl-β-cyclodextrins) show a good affinity for dicationic viologen derivatives in solvents such as acetonitrile or acetone,[6d,9] although the presence of non-competitive counterions (e.g. hexafluorophosphate) is deemed necessary for complexation to occur.[9]

In this communication, it will be shown that per-2,6-di-*O*-methyl-3-*O*-acetyl-β-CD **2**,[10] per-2-*O*-methyl-3,6-di-*O*-acetyl-β-CD **3**,[11] and per-2,6-di-*O*-methyl-3-*O*-benzoyl-β-CD **4**,[12] paired with calix[6]pyrrole **5**[13] can efficiently complex paraquat dichloride **1** in organic media, and can even extract it from water into dichloromethane (Fig. 1).

Preliminary ^{1}H NMR analysis of liquid–solid extraction experiments has shown that a high percentage of solubilisation (>80%) of **1** in CD_3CN or CD_2Cl_2 can be achieved by the combined action of any of the cation receptors **2**–**4** and the anion receptor **5** (Table 1). Since 2 equiv. amounts of anion receptor are required to take up both chloride ions of **1**, extraction experiments were carried out by using a 1:2:1 ratio of **2**–**4**, **5** and **1**,

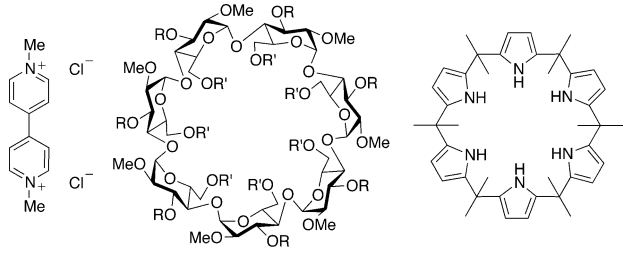

Figure 1. Receptors and substrate employed in the 'binary host' complexation experiments.

Keywords: cyclodextrins; calixpyrroles; inclusion complexes; ion-pair recognition; synergism.

* Corresponding author. Tel.: +39-090-6765242; fax: +39-090-392840; e-mail: gg@isengard.unime.it

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01954-8

Table 1. Solubilisation of paraquat dichloride **1** in CD_3CN and CD_2Cl_2 in the presence of single or paired receptors **2**–**5** at 298 K after 60 min sonication[a]

Host(s)	% of solubilisation in CD_3CN	% of solubilisation in CD_2Cl_2
2	5	12
3	50	<5
4	–[b]	20
5	50	–[c]
2+**5**	~100	80
3+**5**	~100	80
4+**5**	–[b]	~100

[a] Data obtained by ^{1}H NMR analysis, integrating the host(s) and paraquat dichloride signals; percentages are expressed as guest/host ratio.
[b] CD **4** does not dissolve sufficiently in CD_3CN.
[c] Below NMR detection limit.

respectively.[†] Although paraquat dichloride is insoluble in CD_3CN, upon addition of 1 equiv. amount of CDs **2** or **3**—which bind the dication bipyridinium component of the salt—**1** is dissolved up to a 50% extent. Similarly, 50% of **1** is solubilised in the presence of 2 equiv. amount of calix[6]pyrrole **5**, which is known to be an effective receptor for chloride ions.[13] Strikingly, almost quantitative solubilisation of **1** in CD_3CN takes place when the two complementary receptors (i.e. **2**+**5** or **3**+**5**) are simultaneously used. In CD_2Cl_2 the synergic effect of these paired receptors is even more pronounced. In this unsolvating medium, under our experimental and detection (^{1}H NMR) conditions, **1** does not dissolve even in the presence of **5** (2 equiv.). On the other hand, addition of CDs **2**–**4** to a CD_2Cl_2 suspension of **1** causes a modest solubilisation of the salt (5–20%). However, when a CD is paired with **5**, after sonication, 80–100% of the suspended paraquat dichloride is brought into solution.

The solubilisation of solid paraquat dichloride in organic media is driven by host–guest association phenomena, each of the macrocycles used binding its 'complementary ion'. An insight into the solubilisation process is provided by the ^{1}H NMR spectrum of the **3**+**5**+**1** mixture (Fig. 2).

The addition of a mixture of **3** and **5** to a CD_2Cl_2 suspension of **1** results in noticeable spectral changes for both receptors. Complexation of the two chloride

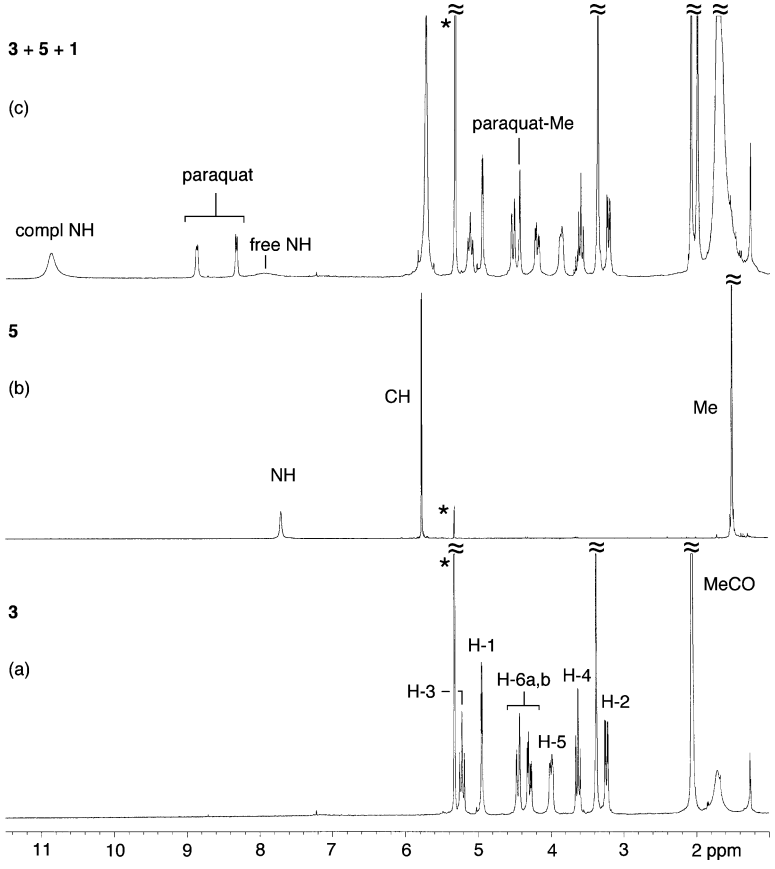

Figure 2. ^{1}H NMR spectra of CD **3** (a), calix[6]pyrrole **5** (b) and a mixture of **3**, **5** and **1** (c) in CD_2Cl_2 at 298 K. An asterisk indicates residual solvent peak.

[†] In a typical experiment, the cation (4 μmol) and anion (8 μmol) receptors were added as solids either separately or together to a suspension of **1** (4 μmol) in 0.8 mL of solvent. Each of these mixtures was sonicated for a fixed time (60 min), filtered to remove any undissolved **1**, and then analysed by ^{1}H NMR spectroscopy. A control experiment showed that the amount of **1** dissolved in either solvent was below the NMR detection limit.

ions of the salt by calix[6]pyrrole is confirmed by the appearance of a broad singlet at $\delta = 10.92$ ppm, assigned to the NH hydrogens of **5** involved in Cl^- binding.[14] The pyrrole CH protons of **5**, which in the free receptor (Fig. 2, trace b) appear as a doublet ($J = 3$ Hz), become a broad singlet and the sharp singlet of the isopropylidene groups at 1.50 ppm turns into a broad singlet at 1.71 ppm upon complexation. Furthermore, the H-3 and H-6a,b hydrogens (which are located in the proximity of the acetyl groups) as well as the acetyl groups of **3** undergo significant complexation induced shifts as a result of the inclusion of the bipyridinium dication inside the complementary CD cavity. Additional ^1H NMR titration experiments, carried out by adding increasing aliquots of paired receptors to a suspension of **1** (in CD_3CN or CD_2Cl_2), were consistent with a slow exchange process for the $Cl^- \subset$ **5** complex (doubling of the peaks for complexed and uncomplexed **5**) on the NMR time-scale, and a fast one for all bipyridinium$^{2+} \subset$CD complexes (progressive up or downfield shift of both the bipyridinium and CDs resonances). In CD_2Cl_2, where the benzoylated CD **4** is totally soluble, the **4**+**5** binary host system is the most effective in the solubilisation of solid **1**. The higher efficiency of **4** over **2** or **3** may be rationalised in terms of more favourable bipyridinium ion/carbonyl group interactions, as a result of a more pronounced electron-donating character of benzoate versus acetate moieties. In addition, the presence of the phenyl groups on the secondary face of CD **4**, may also contribute to extend the cavity of this receptor.

Further evidence for the simultaneous binding of the charged components of **1** by the binary CD/calix[6]pyrrole host systems was provided by the electrospray ionisation mass spectrometry (ESI-MS)[15] of host/guest mixtures (CDs/**5**/**1** in the molar ratio 1:2:1) in acetonitrile. The positive-ion ESI-MS spectra are dominated in all instances by prominent peaks corresponding to the [bipyridinium$\subset$CD]$^{2+}$ superdications (doubly charged molecular ions at $m/z = 905.3$ with **2**, 1122.4 with **3**, and 1003.2 with **4**). Similarly, the negative-ion ESI-MS spectra showed a very intense peak at $m/z = 677.5$, corresponding to the $Cl^- \subset$ **5** superanion (Fig. 3).

The efficiency of the CD/calix[6]pyrrole systems in the complexation of **1** is further demonstrated by liquid–liquid extraction experiments, carried out by using a 1:2:1 molar ratio of **2**–**4**, **5** and **1**, respectively.‡ No paraquat dichloride was detected by ^1H NMR analysis of the CD_2Cl_2 layer either in the blank experiment or when a single receptor was initially present in it. On the other hand, when the binary host systems were used, significant amounts of **1** were extracted (13, 18 and 40%, for the couples **2**+**5**, **3**+**5** and **4**+**5**, respectively).

‡ Extraction experiments of **1** from D_2O into CD_2Cl_2 were carried out by shaking for 1 h at 289 K equal volumes (0.5 mL) of a D_2O solution of **1** (1×10^{-2} M) and a CD_2Cl_2 solution of **2**–**4** (1×10^{-2} M) or **5** (2×10^{-2} M), taken individually or as a mixture of cation and anion receptors.

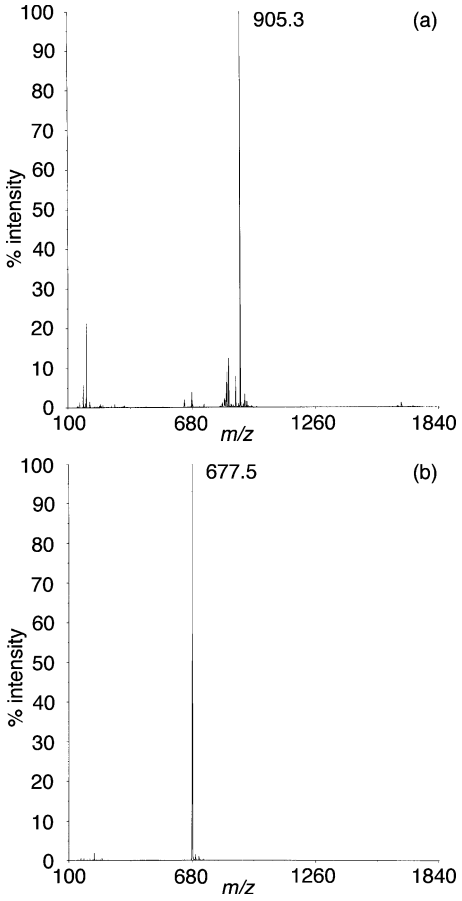

Figure 3. (a) Positive-ion ESI-MS spectrum for the [bipyridinium$\subset$CD]$^{2+}$ complex. (b) Negative-ion ESI-MS spectrum for the $Cl^- \subset$ **5** complex.

To the best of our knowledge, this is the first instance of paraquat dichloride extraction from water into a non-polar organic medium (CD_2Cl_2). The lower efficiency of liquid–liquid versus liquid–solid extraction of **1** can be easily explained in terms of adverse solvating effects due to the presence of D_2O, and reduced activity of the anion binding sites of **5**, involved in hydrogen-bonding with water molecules.[14]

In conclusion, it has been demonstrated that efficient binding of paraquat dichloride in organic solvents, as well as extraction from water into CH_2Cl_2, can be achieved by the use of CD/calix[6]pyrrole binary host systems. The success of this approach relies on the formation of a supramolecular system consisting of one superdication and two superanions ([bipyridinium$\subset$CD]$^{2+}$ and $Cl^- \subset$ **5**, respectively). We believe that these findings will pave the way for the development of analytical procedures of environmental relevance for the removal of **1** from aqueous solutions.

Acknowledgements

This research was financially supported by MURST (PRIN 2000 project).

References

1. (a) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516; (b) Shukla, R.; Kida, T.; Smith, B. D. *Org. Lett.* **2000**, *2*, 3099–3102; (c) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.
2. (a) Deetz, M. J.; Shang, M.; Smith, B. D. *J. Am. Chem. Soc.* **2000**, *122*, 6201–6207; (b) Beer, P. D.; Hopkins, P. K.; McKinney, J. D. *Chem. Commun.* **1999**, 1253–1254; (c) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307–1311.
3. (a) Kavallieratos, K.; Moyer, B. A. *Chem. Commun.* **2001**, 1620–1621; (b) Kavallieratos, K.; Danby, A.; Van Berkel, G. J.; Kelly, M. A.; Sachleben, R. A.; Moyer, B. A.; Bowmann-James, K. *Anal. Chem.* **2000**, *72*, 5258–5264; (c) Kavallieratos, K.; Sachleben, R. A.; Van Berkel, G. J.; Moyer, B. A. *Chem. Commun.* **2000**, 187–188; (d) Murad, M. M.; Hayashita, T.; Shigemori, K.; Nishizawa, S.; Teramae, N. *Anal. Sci.* **1999**, *15*, 1185–1189; (e) Chrisstoffels, L. A. J.; de Jong, F.; Reinhoudt, D. N.; Sivelli, S.; Gazzola, L.; Casnati, A.; Ungaro, R. *J. Am. Chem. Soc.* **1999**, *121*, 10142–10151.
4. Cafeo, G.; Gattuso, G.; Kohnke, F. H.; Notti, A.; Occhipinti, S.; Pappalardo, S.; Parisi, M. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 2122–2126.
5. Monk, P. M. S. *The Viologens*; John Wiley & Sons: Chichester, 1998.
6. (a) Armspach, D.; Gattuso, G.; Königer, R.; Stoddart, J. F. In *Bioorganic Chemistry: Carbohydrates*; Hecht, S. M., Ed.; Oxford University Press: New York, 1999; pp. 458–488, 597–602; (b) Sztejtli, J. *Chem. Rev.* **1998**, *98*, 1743–1754; (c) *Comprehensive Supramolecular Chemistry: Cyclodextrins*; Szejtli, J.; Osa, T., Eds.; Elsevier: Oxford, 1996; Vol. 3; (d) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803–822; (e) Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 846–848.
7. (a) Takahashi, K. *Chem. Rev.* **1998**, *98*, 2013–2034; (b) Hedges, A. R. *Chem. Rev.* **1998**, *98*, 2035–2044; (c) Saenger, W. In *Inclusion Compounds*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 2, pp. 231–259.
8. Rauf Khan, A.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977–1996.
9. (a) Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1959–1976; (b) Wenz, G.; van der Bey, E.; Schmidt, L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 783–785; (c) Wenz, G.; Wolf, F.; Wagner, M.; Kubik, S. *New J. Chem.* **1993**, *17*, 729–738.
10. (a) Hirayama, F.; Mieda, S.; Miyamoto, Y.; Arima, H.; Uekama, K. *J. Pharm. Sci.* **1999**, *88*, 970–975; (b) Keim, W.; Koehnes, A.; Meltzow, W.; Roemer, H. *J. High Resolut. Chromatogr.* **1991**, *14*, 507–529.
11. Icheln, D.; Gehrcke, B.; Piprek, Y.; Mischnick, P.; Koenig, W.; Dessoy, M. A.; Morel, A. F. *Carbohydr. Res.* **1996**, *280*, 237–250.
12. Spencer, C. M.; Stoddart, J. F.; Zarzycki, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1323–1336.
13. (a) Cafeo, G.; Kohnke, F. H.; La Torre, G. L.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1496–1498; (b) Cafeo, G.; Kohnke, F. H.; La Torre, G. L.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **2000**, 1207–1208.
14. Cafeo, G.; Kohnke, F. H.; Parisi, M. F.; Pistone Nascone, R.; La Torre, G. L.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **2002**, *8*, 3148–3156.
15. Schalley, C. A.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568–4579.