ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Pressure effects in the synthesis of isomeric rotaxanes†

Anne Sørensen,[a] Sissel S. Andersen,[a] Amar H. Flood[b] and Jan O. Jeppesen*[a]

Cite this: *Chem. Commun.*, 2013, **49**, 5936

Received 26th March 2013,
Accepted 14th May 2013

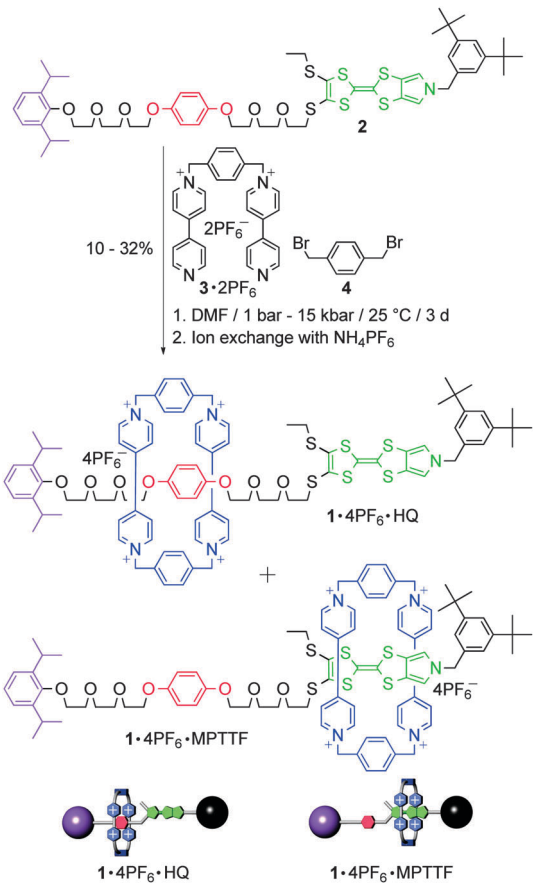
DOI: 10.1039/c3cc42201a

www.rsc.org/chemcomm

Pressure not only influences the yield in the synthesis of a two-station [2]rotaxane, it also determines the distribution of the co-conformational isomers. At high pressure cyclobis(paraquat-*p*-phenylene) is preferentially assembled around a monopyrrolotetrathiafulvalene unit, while at low pressure it is preferentially assembled around a hydroquinone unit.

Incorporating complexity into molecules in the form of stereo, regio, constitutional, configurational and conformational isomers has long motivated the development of new synthetic methods. Mechano-stereochemistry[1] is one of the newest branches of chemistry that is contending with a unique form of isomerism emerging from the interlocked character of its molecular components: co-conformational isomerism. Consider [2]rotaxanes (Scheme 1) as an example in which a ring component is interlocked around a dumbbell.[2] When the [2]rotaxane has two different recognition sites along its dumbbell, as is typical for molecular switches,[3] it can exist as one of two co-conformational (or translational[4]) isomers; the ring can be situated at one of the two stations. The isomeric relationship of co-conformations is akin to the *E*/*Z* isomerism of two functional groups substituted around an olefin.[5] With that likeness in mind, being able to dictate the ring's localisation on one of two stations in a non-degenerate [2]rotaxane upon command provides an opportunity to isolate one or both of the two possible co-conformational isomers. Ultimately, such control will allow for the creation of artificial molecular machines with enhanced complexity.[6] One such outcome was demonstrated using thermodynamic control over the relative stabilities of the two stations in a rotary molecular motor.[7] An alternative approach, which we discovered during a typical pressure-induced reaction,[8,9] was the use of pressure as a physical parameter to access kinetic control over the ratio of co-conformational isomers produced in the formation of a [2]rotaxane.

Here, we describe how pressure not only influences the yield in the synthesis of a two-station [2]rotaxane but that it also determines the product distribution between the two possible co-conformational isomers. The [2]rotaxane **1**·4PF$_6$ (Scheme 1) is based on a dumbbell containing monopyrrolotetrathiafulvalene (MPTTF) and hydroquinone (HQ) stations for encirclement by cyclobis(paraquat-*p*-phenylene) tetrakis(hexafluorophosphate) (CBPQT·4PF$_6$). An S-Et group situated between the two stations acts as an effective barrier[10] to enable measurement of the relative amount of each isomer. The synthesis (Scheme 1) of the [2]rotaxane isomers **1**·4PF$_6$·HQ and **1**·4PF$_6$·MPTTF



Scheme 1 Synthesis of the two co-conformational isomeric [2]rotaxanes **1**·4PF$_6$·HQ and **1**·4PF$_6$·MPTTF together with their cartoon representations.

[a] *Department of Physics, Chemistry, and Pharmacy, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark. E-mail: joj@sdu.dk*
[b] *Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405, USA*

† Electronic supplementary information (ESI) available: Experimental procedures, spectral characterisation data, and description of the determination of binding constants. See DOI: 10.1039/c3cc42201a

Table 1 Distribution of the co-conformational isomers **1**·4PF$_6$·HQ and **1**·4PF$_6$·MPTTF after synthesis at different pressures[a]

Pressure	Yield	**1**·4PF$_6$·HQ : **1**·4PF$_6$·MPTTF[b]	Colour[c]
1 bar	10%	73 : 27	Light brown
5 kbar	31%	53 : 47	↓
10 kbar	32%	42 : 58	
15 kbar	31%	26 : 74	Green

[a] Syntheses were carried out with 1 equiv. dumbbell **2** (30 mM), 3 equiv. **3**·2PF$_6$ and 3 equiv. dibromide **4** in anhydrous DMF at 25 °C. [b] The ratios were found using ^{1}H NMR spectroscopy (ESI). [c] The colour of the mixtures of **1**·4PF$_6$·HQ and **1**·4PF$_6$·MPTTF in MeCN at 25 °C.

was carried out using the dumbbell compound **2** as the template for the formation of CBPQT·4PF$_6$ from **3**·2PF$_6$[11] and **4**. The clipping reaction was carried out in DMF at 25 °C for three days with the effect of pressure examined from 1 bar to 15 kbar. Following counter ion exchange, the two isomeric [2]rotaxanes were isolated in overall yields of 10–32% in two steps. By analysing the purified product, it was observed that **1**·4PF$_6$ exists as a mixture of the two possible co-conformational isomers, **1**·4PF$_6$·HQ and **1**·4PF$_6$·MPTTF. The solutions of these two isomers are red and green in colour which is due to characteristic charge-transfer (CT) UV-Vis-NIR absorption bands centred at 490 and 820 nm, respectively (ESI,† Fig. S1).

The population ratios (Table 1, ESI,† Fig. S4) were determined from the ^{1}H NMR spectra (25 °C, CD_3CN). Several protons in both the dumbbell component and CBPQT·4PF$_6$ give rise to two sets of signals, one for each of the two isomers. Overall, the yield increases when the pressure is increased,[12] and furthermore, the amount of **1**·4PF$_6$·MPTTF increases as a function of pressure faster than the amount of **1**·4PF$_6$·HQ resulting in an inversion of the ratio between the two isomeric [2]rotaxanes. By plotting (Fig. 1) the ratio of **1**·4PF$_6$·HQ : **1**·4PF$_6$·MPTTF against the pressure a linear relationship between pressure and the distribution of the co-conformational isomers is obtained. Based on these results, it is evident that **1**·4PF$_6$·HQ is favoured at ambient pressure whereas **1**·4PF$_6$·MPTTF is favoured at high pressure.

The [2]rotaxane **1**·4PF$_6$ contains both a HQ and a MPTTF binding site and to get a better understanding of how these units influence the isomeric distribution, two model [2]rotaxanes **5**·4PF$_6$ and **6**·4PF$_6$ (Fig. 2) were synthesised (ESI†). The respective dumbbell compounds were mixed together with **3**·2PF$_6$ and the dibromide **4** to investigate the product distribution **5**·4PF$_6$: **6**·4PF$_6$ as a function of pressure. The clipping reaction was carried out in DMF at 25 °C for three days with a pressure of 1 bar or 10 kbar. Following counter ion exchange, combined yields of 7% or 24%[12] for the two steps were obtained.

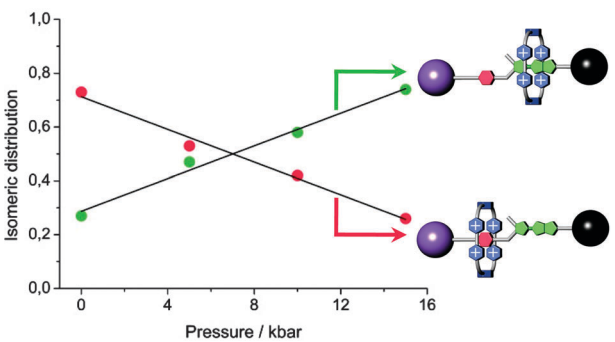


Fig. 1 A graphical representation illustrating the pressure dependency of the isomeric distribution within [2]rotaxane **1**·4PF$_6$.

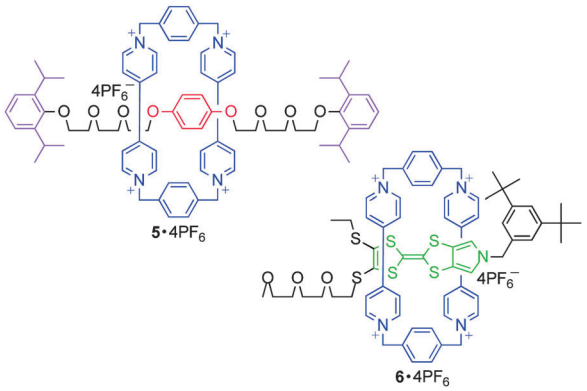


Fig. 2 Structural formulae of the [2]rotaxanes **5**·4PF$_6$ and **6**·4PF$_6$.

After purification, a mixture of the two possible products, **5**·4PF$_6$ and **6**·4PF$_6$, was observed. These two products give rise to characteristic CT absorption bands centred at 460 and 820 nm, respectively (ESI,† Fig. S5). The population ratio between the two products (Table 2) was determined from the ^{1}H NMR spectrum (ESI,† Fig. S9). As in the case of the [2]rotaxane **1**·4PF$_6$, the results reveal that pressure has a strong impact on the product distribution. The amount of **6**·4PF$_6$ increases relative to the amount of **5**·4PF$_6$ showing that the HQ rotaxane is favoured as the product at ambient pressure whereas the MPTTF rotaxane can be selectively accessed at high pressure.

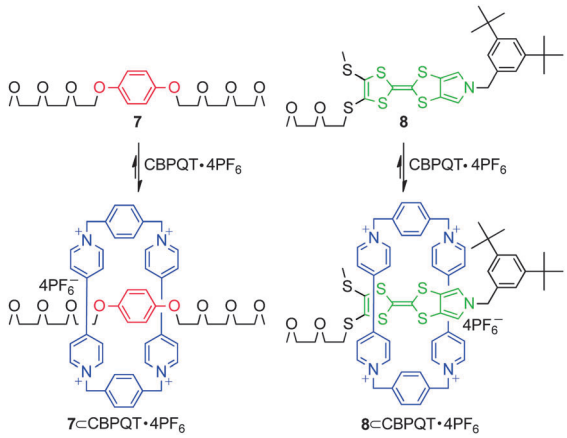
It is clear that the rotaxanes with the HQ station located inside the cavity of CBPQT·4PF$_6$ are favoured at ambient pressure while those with the MPTTF station inside the cavity of CBPQT·4PF$_6$ are favoured at high pressure. To help support this observation further, the binding affinities of two model host–guest systems (Scheme 2) were investigated. Mixing the dumbbell compounds **7** or **8** (syntheses; ESI†) with equimolar amounts of CBPQT·4PF$_6$[11] at 25 °C in DMF leads to the formation of [2]pseudorotaxanes **7**⊂CBPQT·4PF$_6$ and **8**⊂CBPQT·4PF$_6$, respectively. **7**⊂CBPQT·4PF$_6$ is formed immediately as evident by the formation of a red solution and the concomitant appearance of a CT band at 464 nm.[13] Both observations are characteristic of superstructures in which HQ derivatives are being complexed inside the cavity of CBPQT·4PF$_6$.[11] The formation of **8**⊂CBPQT·4PF$_6$ can be followed visually over time by the slow evolution of a green solution after mixing the components.[14] A concomitant appearance of a CT absorption band centered at 783 nm is characteristic of superstructures in which MPTTF derivatives are complexed inside the cavity of CBPQT·4PF$_6$.[15] By employing the UV/Vis dilution method (ESI†),[15] the binding affinities (K_a, $\Delta G°$) at 25 °C in DMF were determined (Table 3).

The binding of **7** with CBPQT·4PF$_6$ is stronger than with **8**. This result is not expected on account of the fact that MPTTF is a stronger π-electron donor than HQ.[11,15] Previous NMR studies carried out in CD_3CN on a similar MPTTF system without the

Table 2 Distribution of **5**·4PF$_6$ and **6**·4PF$_6$ after synthesis at different pressures[a]

Pressure	Yield	**5**·4PF$_6$: **6**·4PF$_6$[b]	Colour[c]
1 bar	7%	85 : 15	Brown
10 kbar	24%	39 : 61	Green

[a] Syntheses were carried out with 1 equiv. dumbbell **S10** (30 mM), 1 equiv. dumbbell **S13** (30 mM), 3 equiv. **3**·2PF$_6$, and 3 equiv. dibromide **4** in anhydrous DMF at 25 °C. [b] The ratios were found using ^{1}H NMR spectroscopy (ESI). [c] The colour of the mixtures of **5**·4PF$_6$ and **6**·4PF$_6$ in MeCN at 25 °C.



Scheme 2 Formation of the two [2]pseudorotaxanes **7**⊂CBPQT·4PF$_6$ and **8**⊂CBPQT·4PF$_6$.

Table 3 Comparison of binding constants (K_a values)[a] and derived free energies of complexation ($-\Delta G^\circ$)[a] between CBPQT·4PF$_6$ and **7** or **8**

Complex	λ_{max} [nm]	K_a[b] [M^{-1}]	$-\Delta G^\circ$[b] [kcal mol^{-1}]
7⊂CBPQT·4PF$_6$	464	300 ± 50	3.42 ± 0.08
8⊂CBPQT·4PF$_6$	783	100 ± 10	2.61 ± 0.06

[a] The values were determined using absorption spectroscopy at 25 °C in DMF. [b] The errors were obtained as described in ref. 16.

stopper group reveal that CBPQT·4PF$_6$ is shifted a little towards the pyrrole ring. In the present molecule, the 3,5-di-*t*-butyl-benzene stopper is attached directly to the pyrrole ring making it difficult to obtain the optimal geometry of the superstructure. We believe that this change in geometry weakens the binding between the two components to such a degree that the poorer HQ π-electron donor binds stronger to CBPQT·4PF$_6$. Furthermore, **7** contains two ethylene glycol chains while **8** bears only one. It has been reported previously[16] that ethylene glycol chains have a significant influence on the binding to CBPQT·4PF$_6$ in $(Me)_2CO$, and a greater number of ethylene glycol chains enhances the binding affinity. All these factors make the non-covalent interactions in **7**⊂CBPQT·4PF$_6$ stronger than those in **8**⊂CBPQT·4PF$_6$.

Based on prior work,[9] it is reasonable to assume that the difference between the binding affinities obtained in the two [2]pseudorotaxanes **7**⊂CBPQT·4PF$_6$ and **8**⊂CBPQT·4PF$_6$ represents the energy differences in [2]rotaxane **1**·4PF$_6$. It is therefore possible to determine the theoretical thermodynamic ratio between the co-conformational isomers **1**·4PF$_6$·HQ and **1**·4PF$_6$·MPTTF.[17] At 25 °C, a $K_{HQ/MPTTF}$ value of 3.9 is obtained corresponding to a ratio of 80 : 20 between **1**·4PF$_6$·HQ and **1**·4PF$_6$·MPTTF, which is comparable to the ratio of 73 : 27 (Table 1) obtained from the experiments conducted at ambient pressure. In addition, the theoretical ratio of 80 : 20 is close to the results obtained for the two [2]rotaxanes **5**·4PF$_6$ and **6**·4PF$_6$, where ^{1}H NMR spectroscopy provided a 85 : 15 ratio between **5**·4PF$_6$ and **6**·4PF$_6$ at 1 bar. These findings indicate that **1**·4PF$_6$·HQ is the thermodynamically most stable product and that the clipping reaction is under kinetic control. In addition, the experiments indicate that the rate constant for the formation of **1**·4PF$_6$·MPTTF increases faster than the rate constant for the formation of **1**·4PF$_6$·HQ when the pressure is increased, *i.e.*, the activation volume for the formation of **1**·4PF$_6$·MPTTF is more negative as compared to **1**·4PF$_6$·HQ.

In conclusion, we have synthesised and characterised the two different co-conformational isomers of the [2]rotaxane **1**·4PF$_6$. By adjusting the pressure during the synthesis, it is possible to direct the location of the CBPQT·4PF$_6$ ring to either the HQ or the MPTTF recognition site. At high pressure, CBPQT·4PF$_6$ is preferentially assembled around the MPTTF unit, whereas at low pressure the preference rests with the assembly around the HQ station. The findings reported in this communication are, to the best of our knowledge, the first example where pressure is used as a physical parameter to access kinetic control over the ratio of co-conformational isomers produced in the formation of a [2]rotaxane by the clipping of a macrocycle around a two-station dumbbell.

This work has been supported by the Villum Foundation and The Danish Natural Science Research Council (FNU, project no. 11-106744). We thank Marcel Schmidt and Gitte Sørensen for the synthesis of some of the starting materials.

Notes and references

1 M. A. Olson, Y. Y. Botros and J. F. Stoddart, *Pure Appl. Chem.*, 2010, **82**, 1569.
2 (*a*) F. Durola, J. Lux and J.-P. Sauvage, *Chem.–Eur. J.*, 2009, **15**, 4124; (*b*) S.-Y. Hsueh, C.-T. Kuo, T.-W. Lu, C.-C. Lai, Y.-H. Liu, H.-F. Hsu, S.-M. Peng, C.-h. Chen and S.-H. Chiu, *Angew. Chem., Int. Ed.*, 2010, **49**, 9170; (*c*) G. Barin, A. Coskun, D. C. Friedman, M. A. Olson, M. T. Colvin, R. Carmielli, S. K. Dey, O. A. Bozdemir, M. R. Wasielewski and J. F. Stoddart, *Chem.–Eur. J.*, 2011, **17**, 213; (*d*) T. Pierro, C. Gaeta, C. Talotta, A. Casapullo and P. Neri, *Org. Lett.*, 2011, **13**, 2650.
3 E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2007, **46**, 72.
4 Translational isomer has been advocated for rotaxanes and circumrotational isomer for catenanes but co-conformational isomer is a more general term for use with any interlocked molecule[2].
5 (*a*) D. M. Walba, *Tetrahedron*, 1985, **41**, 3161; (*b*) C. O. Dietrich-Buchecker and J.-P. Sauvage, *Chem. Rev.*, 1987, **87**, 795; (*c*) J. F. Stoddart, *Chem. Soc. Rev.*, 2009, **38**, 1802.
6 (*a*) A. H. Flood, R. J. A. Ramirez, W.-Q. Deng, R. P. Muller, W. A. Goddard III and J. F. Stoddart, *Aust. J. Chem.*, 2004, **57**, 301; (*b*) M. S. Vickers and P. D. Beer, *Chem. Soc. Rev.*, 2007, **36**, 211.
7 J. V. Hernandez, E. R. Kay and D. A. Leigh, *Science*, 2004, **306**, 1532.
8 (*a*) R. Ballardini, V. Balzani, W. Dehaen, A. Dell'Erba, F. Raymo, J. Stoddart and M. Venturi, *Eur. J. Org. Chem.*, 2000, 591; (*b*) S. Nygaard, B. Laursen, T. Hansen, A. Bond, A. Flood and J. Jeppesen, *Angew. Chem., Int. Ed.*, 2007, **46**, 6093; (*c*) Y. Tokunaga, N. Wakamatsu, N. Ohiwa, O. Kimizuka, A. Ohbayashi, K. Akasaka, S. Saeki, K. Hisada, T. Goda and Y. Shimomura, *J. Org. Chem.*, 2010, **75**, 4950.
9 J. W. Choi, A. H. Flood, D. W. Steuerman, S. Nygaard, A. B. Braunschweig, N. N. P. Moonen, B. W. Laursen, Y. Luo, E. DeIonno, A. J. Peters, J. O. Jeppesen, K. Xu, J. F. Stoddart and J. R. Heath, *Chem.–Eur. J.*, 2006, **12**, 26.
10 S. Nygaard, B. W. Laursen, A. H. Flood, C. N. Hansen, J. O. Jeppesen and J. F. Stoddart, *Chem. Commun.*, 2006, 144.
11 P. L. Anelli, P. R. Ashton, R. Ballardini, V. Balzani, M. Delgado, M. T. Gandolfi, T. T. Goodnow, A. E. Kaifer and D. Philp, *J. Am. Chem. Soc.*, 1992, **114**, 193.
12 This pressure dependency is well known in the synthesis of ionic species of several catenanes and rotaxanes based on CBPQT·4PF$_6$[8,9].
13 As expected, the exchange between the complexed and uncomplexed species in a 1 : 1 mixture of **7** and CBPQT·4PF$_6$ occurs rapidly on the ^{1}H NMR time scale at 25 °C.
14 Due to the S-Me group on the MPTTF derivative **8**, the exchange between the complexed and uncomplexed species in a 1 : 1 mixture of **8** and CBPQT·4PF$_6$ occurs slowly on the ^{1}H NMR time scale at 25 °C. For that reason the mixture was prepared 1 hour before use to ensure equilibrium is established.
15 M. B. Nielsen, J. O. Jeppesen, J. Lau, C. Lomholt, D. Damgaard, J. P. Jacobsen, J. Becher and J. F. Stoddart, *J. Org. Chem.*, 2001, **66**, 3559.
16 S. Nygaard, C. N. Hansen and J. O. Jeppesen, *J. Org. Chem.*, 2007, **72**, 1617.
17 Determined using the equation $K_{HQ/MPTTF} = \exp(-\Delta\Delta G^\circ/RT)$.

