Synthesis and solid state structure of a hydrazone-disulfide macrocycle and its dynamic covalent ring-opening under acidic and basic conditions†

Max von Delius,[a] Edzard M. Geertsema,[a] David A. Leigh*[a] and Alexandra M. Z. Slawin[b]

Received 4th June 2010, Accepted 8th July 2010
DOI: 10.1039/c0ob00214c

The synthesis and characterisation, including solid state structure, of a macrocycle containing both a hydrazone and a disulfide linkage is described. Selective ring-opening of the macrocycle under thermodynamic control could be achieved at either the disulfide or the hydrazone linkage by applying mutually exclusive sets of reaction conditions.

Introduction

The chemistry of covalent bonds that are dynamic under particular conditions has attracted considerable interest over the past decade.[1] When the components of a dynamic chemical system are interconnected by several types of reversible exchange reactions—rather than just one—complex behaviour of the molecular network can emerge, a phenomenon that lies at the core of systems chemistry.[2] To date several such multi-level constitutionally dynamic[3] systems have been described.[4] In these systems the various exchange processes can relate to each other in one of two ways: (i) orthogonal,[4a] where the exchange reactions do not interfere with each other; and (ii) communicating,[4b] where the products of the exchange reactions cross over and influence the outcome of the other. Adding a further level of control by having the reactions no longer occur concurrently could prove useful for ratcheting the distribution away from the thermodynamic minimum,[5] a feature useful for—amongst other things—the development of new molecular motor systems.[6] To achieve this the conditions under which the different exchange reactions occur need to be mutually exclusive. In a double-level[7] system this requires that under one set of conditions only one of the two bond types is dynamic and the other is kinetically locked, and that under a second set of conditions the relative rates of bond forming/breaking are reversed.

In recent independent studies, the groups of Furlan[8a] and Otto[8b] described simple (acyclic) substrates containing a disulfide and hydrazone moiety that undergo reversible exchange reactions under different sets of reaction conditions. We were interested in the implications of applying reactions that occur under mutually exclusive conditions to a cyclic substrate featuring such linkages .[8] Aside from establishing a viable synthetic route to such systems, our aim was to investigate the dynamic covalent ring-opening of such a macrocycle in a situation where fully reversible intra- and intermolecular exchange processes compete. Here we report on the synthesis (Scheme 1) and dynamic chemistry (Fig. 1, Fig. 2 and Scheme 2) of macrocycle $\mathbf{1}_1$,[9] which contains both a hydrazone and a disulfide unit within the bonds that make up the ring. We demonstrate selective ring-opening of $\mathbf{1}_1$ at either the disulfide or the hydrazone moiety by reversible covalent bond formation under two sets of mutually exclusive reaction conditions (acidic and basic).

We probe the dynamic chemistry of $\mathbf{1}_1$ through three types of experiments, each carried out under thermodynamic control: First, we treated $\mathbf{1}_1$ with acid or base conditions to demonstrate that under either set of conditions reversible covalent bond formation gives rise to a mixture of cyclic oligomers of type $\mathbf{1}_n$[9] (Fig. 1). Second, $\mathbf{1}_1$ was treated with an acyclic disulfide or hydrazone scavenger, in the presence of acid or base, to demonstrate that the disulfide bonds exchange only under basic conditions and the hydrazone bonds exchange only under acidic conditions (Scheme 2 and Fig. 2). Finally, $\mathbf{1}_1$ was subjected to basic or acidic conditions in the presence of both a disulfide *and* a hydrazone scavenger (Fig. 3) to demonstrate that each dynamic exchange reaction is not affected by the presence of the other building blocks (which are inactive under the other's set of reaction conditions).

Results and discussion

Synthesis of macrocycle $\mathbf{1}_1$

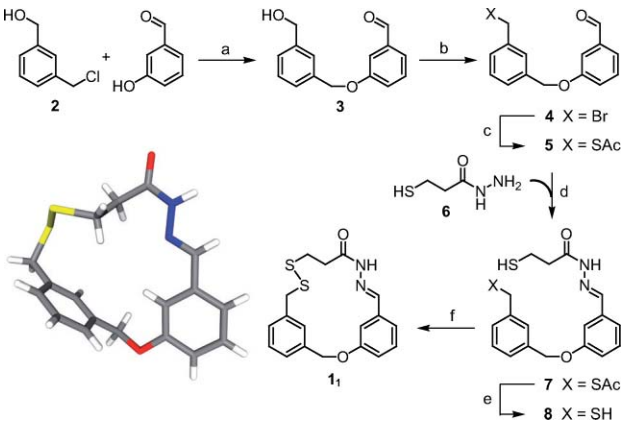
Macrocycle $\mathbf{1}_1$ was prepared according to the route shown in Scheme 1. Bis-aromatic scaffold **3** was obtained from benzylic chloride **2** and 3-hydroxybenzaldehyde *via* Williamson ether synthesis (step a). Alcohol **3** was converted into bromide **4**, followed by nucleophilic substitution with potassium thioacetate. Condensation of hydrazide **6** with aldehyde **5** yielded hydrazone **7** (step d). The synthesis was completed by sodium methoxide mediated deprotection of the thioacetate group and oxidative ring-closure using iodine, which provided macrocycle $\mathbf{1}_1$ in 56% yield.[10]

Solid state structure of macrocycle $\mathbf{1}_1$

Single crystals of $\mathbf{1}_1$ suitable for X-ray crystallography were obtained by slow cooling of a hot saturated solution of $\mathbf{1}_1$ in ethanol. The solid state structure revealed several interesting features of macrocycle $\mathbf{1}_1$ (Scheme 1): the two aromatic rings are almost orthogonal (torsion angle 94°) and the hydrazone double bond is in the *E* configuration (also shown by ^{1}H NMR studies in $CDCl_3$) and planar (conjugated) with the adjacent aromatic

[a]*School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh, UK EH9 3JJ. E-mail: David.Leigh@ed.ac.uk; Fax: +44 131 650 6453; Tel: +44 131 650 4721*
[b]*School of Chemistry, University of St. Andrews, Purdie Building, St. Andrews, Fife, UK KY16 9ST*

† Electronic supplementary information (ESI) available: ^{1}H NMR spectra of all synthesised compounds. CCDC reference number 783640. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00214c



Scheme 1 Synthesis and X-ray crystal structure of macrocycle $\mathbf{1}_1$. Reaction conditions: (a) NaH, DMF, RT, 3 h, 83%; (b) $SOBr_2$, benzene, RT, 36 h, 73%; (c) KSAc, DMF, RT, 12 h, 95%; (d) AcOH (cat.), MeOH, RT, 3 h, 88%; (e) NaOMe, MeOH, RT, 2 h, 78%; (f) I_2, MeOH–CH_2Cl_2, 0 °C, 30 min, 56%. Bottom left: Solid state structure of $\mathbf{1}_1$ determined by single crystal X-ray diffraction. C: grey, H: white, O: red, N: blue, S: yellow. Selected bond lengths [Å] and angles [°]: S–S 2.0335(11); N–N 1.376(3); C–S–S–C 100.92(13).

ring. The C–S–S–C torsion angle (101°) deviates by 11° from the 90° angle typically found[11] for such functional groups and the two adjacent methylene groups between the disulfide and the hydrazone moiety are closer to an eclipsed than to a staggered conformation (dihedral angle 137°). These observations suggest that the presence of the three rigid elements (two aromatic rings and the acyl hydrazone) in the macrocycle result in a significant amount of ring strain in $\mathbf{1}_1$.

Dynamic Chemistry I: Oligomerisation of macrocycle $\mathbf{1}_1$ in the absence of scavengers

To investigate different aspects of the dynamic chemistry of macrocycle $\mathbf{1}_1$, we carried out three types of experiments that involved macrocycle ring-opening under thermodynamic control. In the first experimental series we subjected $\mathbf{1}_1$ to different chemical reagents (trifluoroacetic acid-d_1 (TFA-d_1), triethylamine (Et_3N), diazabicyclo-[5,4,0]undec-7-ene (DBU), DL-dithiothreitol (DTT)),[8,12] solvents ($CDCl_3$, DMSO-d_6) and reaction temperatures (RT, 55 °C), in order to find effective conditions for cyclooligomerisation *via* reversible disulfide and hydrazone exchange (see Fig. 1a). Deuterated solvents were employed to enable the progress of reactions to be followed by ^{1}H NMR spectroscopy.

Acid-mediated oligomerisation proved efficient at room temperature in $CDCl_3$ (one day equilibration time) using five equivalents of TFA-d_1 and millimolar initial concentrations of substrate ($\mathbf{1}_1$). Base-induced oligomerisation was most efficient (two days equilibration time at room temperature) in $CDCl_3$ employing the strong base DBU (1.0 equiv.) and DTT (0.1 equiv.) as a catalytic reducing agent (Fig. 1a). Hydrazone exchange did not occur using DMSO-d_6 and disulfide exchange was extremely slow (equilibration time more than 7 days at 55 °C) when the weaker base triethylamine was employed. Under the two most efficient sets of acidic and basic conditions (TFA-d_1 in $CDCl_3$ and DBU/DTT in $CDCl_3$), small, but detectable amounts (see ESI for a typical ^{1}H NMR spectrum†) of dimeric ($\mathbf{1}_2$), trimeric ($\mathbf{1}_3$) and tetrameric ($\mathbf{1}_4$) macrocyclic analogues[13] of $\mathbf{1}_1$ were found in the equilibrium

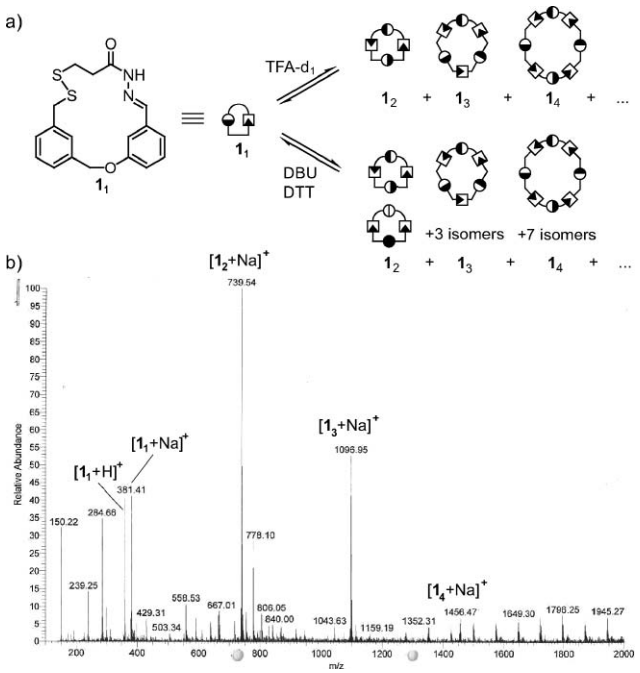


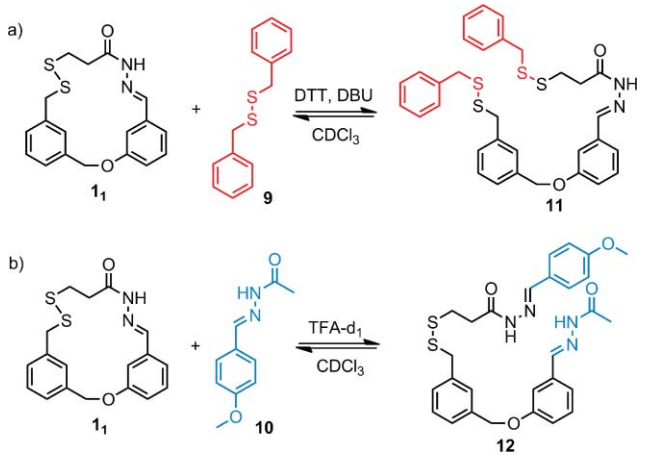
Fig. 1 (a) Two sets of reaction conditions for the efficient conversion of macrocycle $\mathbf{1}_1$ into a distribution of cyclic oligomers $\mathbf{1}_n$ by dynamic covalent bond formation:[13] (acidic) $\mathbf{1}_1$ (7.0 µmol, 1 equiv.), 0.5 mL $CDCl_3$, TFA-d_1 (35 µmol, 5 equiv.) 1 day, RT; (basic) $\mathbf{1}_1$ (7.0 µmol, 1 equiv.), 0.5 mL $CDCl_3$, DBU (7 µmol, 1 equiv.) and DTT (0.7 µmol, 0.1 equiv.), 2 days, RT. (b) ESI$^+$ mass spectrum of an equilibrium mixture containing $\mathbf{1}_1$ and higher oligomers $\mathbf{1}_n$ after treatment of $\mathbf{1}_1$ in $CDCl_3$ under acidic conditions: $\mathbf{1}_1$ (7.0 µmol, 1 equiv.), 0.5 mL $CDCl_3$, TFA-d_1 (35 µmol, 5 equiv.) 1 day, RT. Note: The mass spectrum gives a disproportionate bias to higher oligomeric macrocycles, which appear to bind to Na^+ more effectively than $\mathbf{1}_1$. See ESI† for the corresponding ^{1}H NMR spectrum which shows that, in fact, <5% oligomers higher than $n = 1$ are present in the reaction mixture.

mixtures after an equilibration time of 1–2 days at RT (after which time the composition of the reaction mixtures no longer changed) as confirmed by electrospray ionisation-mass spectrometry (ESI-MS) (Fig. 1b). (Note: the two mixtures resulting from acidic or basic conditions should not be identical—experimental evidence for this was provided by slight differences in the ^{1}H NMR spectra—because disulfide exchange can result in a higher number of constitutional isomers for each group of cyclic oligomers $\mathbf{1}_n$ with $n > 1$; see Fig. 1a.[13])

Dynamic Chemistry II: Ring-opening of macrocycle $\mathbf{1}_1$ in the presence of a single disulfide or hydrazone scavenger

A second series of experiments was conducted with the objective of confirming which functional group was dynamic under which set of conditions, opening macrocycle $\mathbf{1}_1$ at either the disulfide or at the hydrazone linkage in the presence of acyclic 'scavenger' molecules (Scheme 2).

For disulfide exchange the symmetric benzylic disulfide **9** was used as the scavenger (Scheme 2a) and for hydrazone exchange the scavenger employed was acyl hydrazone **10** (Scheme 2b). First, the optimised basic conditions determined from the dynamic experiments in the absence of scavengers (initial concentration of $\mathbf{1}_1$ 12 mM, $CDCl_3$, 1.0 equiv. DBU and 0.1 equiv. DTT, RT,



Scheme 2 Dynamic covalent ring-opening of macrocycle $\mathbf{1}_1$ in the presence of an acyclic disulfide or hydrazone scavenger. (a) Disulfide exchange of macrocycle $\mathbf{1}_1$ (59 µmol, 1 equiv.) with disulfide scavenger **9** (0.29 mmol, 5 equiv.) under basic conditions (DBU, 59 µmol, 1 equiv.; DTT, 5.9 µmol, 0.1 equiv.) in $CDCl_3$ (5 mL, initial concentration of $\mathbf{1}_1$ 12 mM) after 24–48 h at RT led to an equilibrium mixture of $\mathbf{1}_1$, **9** and ring-opened product **11** (molar ratios: $\mathbf{1}_1$:**9**:**11** 13 : 82 : 5). (b) Acid-mediated (TFA-d_1, 0.29 mmol, 5 equiv.) hydrazone exchange of macrocycle $\mathbf{1}_1$ (59 µmol, 1 equiv.) with hydrazone scavenger **10** (0.29 mmol, 5 equiv.) in $CDCl_3$ (5 mL, initial concentration of $\mathbf{1}_1$ 12 mM) after 6–12 h at RT led to an equilibrium mixture of $\mathbf{1}_1$, **10** and ring-opened product **12** (molar ratios $\mathbf{1}_1$:**10**:**12** 13 : 82 : 5). Note: Small amounts of oligomers (<5% as indicated by ^{1}H NMR) were also present in the equilibrium mixtures.

1–2 days) were applied to a mixture of $\mathbf{1}_1$ and an excess (5 equiv.) of **9** (Scheme 2a), resulting in formation of **11** in 28% isolated yield (along with $\mathbf{1}_1$ and small amounts of higher cyclic and open-chain oligomers). In a separate experiment $\mathbf{1}_1$ was subjected to the optimised acidic conditions (initial concentration of $\mathbf{1}_1$ 12 mM, $CDCl_3$, 5 equiv. of TFA-d_1, RT, 6–12 h) in the presence of an excess (5 equiv.) of hydrazone scavenger **10** (Scheme 2b), which gave **12** in 26% isolated yield (along with small amounts of oligomeric species).

When only one equivalent of scavenger was used, **11** and **12** were each formed as roughly 5% of the product mixture (as determined by ^{1}H NMR) under the basic and acidic conditions, respectively (see Fig. 2a). To prove that these mixtures were indeed at thermodynamic minimum, pristine ring-opened products **11** and **12** in the absence of scavenger were subjected to basic (**11**) or acidic (**12**) conditions in two 'reverse-equilibration' experiments (Fig. 2).

Fig. 2b shows the conversion of **11** back into $\mathbf{1}_1$ as monitored by ^{1}H NMR spectroscopy. Starting from pure **11**, a 95% conversion into macrocycle $\mathbf{1}_1$ was observed over 24 h under the standard basic conditions (Fig. 2a). Similarly **12** was converted back into $\mathbf{1}_1$ in approximately 95% yield under acidic conditions. These results confirmed that under the basic and acidic reaction conditions an ~95 : 5 molar ratio of macrocycle to ring-opened product corresponds to the thermodynamic minimum of the system (at a substrate concentration of 12 mM in $CDCl_3$ at RT). The ^{1}H NMR spectrum displayed at the front of Fig. 2b also shows minor peaks indicative of higher cyclic oligomers, $\mathbf{1}_n$ ($n > 1$). The total amount of these oligomers did not exceed ~5% of the mixture.

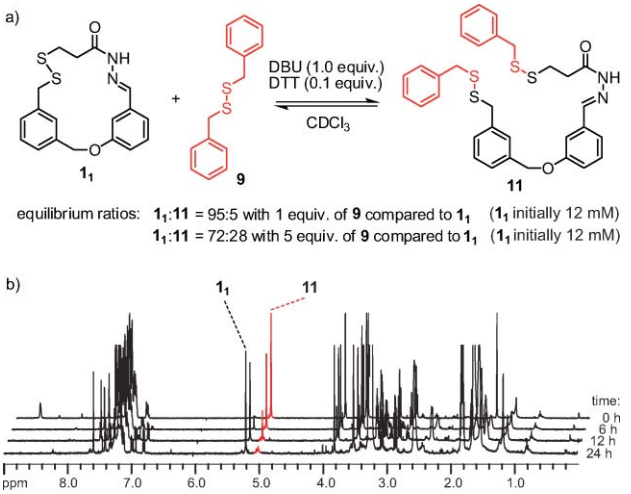


Fig. 2 (a) Composition of equilibrium between $\mathbf{1}_1$, **9** (1 or 5 equiv.) and **11**. Reaction conditions: Initial concentration of $\mathbf{1}_1$ or **11**: 12 mM, DBU (1 equiv.), DTT (0.1 equiv.), RT, 24–48 h. (b) ^{1}H NMR monitoring of reverse-equilibration experiment (initial concentration of **11** 12 mM). Pristine ring-opened product **11** (rear spectrum) was converted back into a mixture containing predominantly macrocycle $\mathbf{1}_1$ ($\mathbf{1}_1$:**11** ~95 : 5) (front spectrum). The signals for the methylene groups in the ether linkages (in the region δ = 5.0–5.15 ppm), which differ significantly in chemical shift in $\mathbf{1}_1$ and **11**, are highlighted.

Dynamic Chemistry III: Competition experiments with macrocycle $\mathbf{1}_1$ in the presence of both disulfide and hydrazone scavengers 9 and 10

Fig. 3a shows a third series of experiments on the dynamic ring-opening of macrocycle $\mathbf{1}_1$. In a competition experiment, a mixture of macrocycle $\mathbf{1}_1$ and both scavenger compounds **9** (5 equiv.) and **10** (5 equiv.) was subjected to the optimised conditions for either, (i), disulfide or, (ii), hydrazone exchange (see experimental section for reaction conditions). HPLC analysis (Fig. 3b) of the resulting mixtures revealed that under basic conditions only ring-opened compound **11** (resulting from disulfide exchange) was obtained (yellow peak in trace (i)), whereas **12** (which would arise from hydrazone exchange) was not observed. Under acidic conditions the opposite result occurred, hydrazone-exchanged ring-opened product **12** (purple peak in trace (ii)) was formed without any of **11**. As in the previous experiments, ^{1}H NMR indicated the presence of a small amount (<5%) of oligomers formed as byproducts under the reaction conditions. These results confirm that conditions (i) and (ii) are, indeed, mutually exclusive with respect to the dynamic covalent exchange processes that they induce. Basic conditions, (i), promote disulfide exchange and preclude hydrazone exchange and *vice versa*: acidic conditions, (ii), induce hydrazone exchange and preclude disulfide exchange. Equally importantly, neither set of conditions are affected by the presence of the scavenger that does not undergo dynamic exchange under those conditions.

The macrocyclic hydrazone-disulfide system is subject to different entropic considerations to the previously studied acyclic systems.[8] This is apparent in the remarkable dependence of the equilibrium composition on concentration. For example, we were only able to obtain HPLC trace (ii) shown in Fig. 3b when hydrazone exchange was quenched in the concentrated reaction mixture (12 mM in $CDCl_3$) by addition of Et_3N prior to dilution

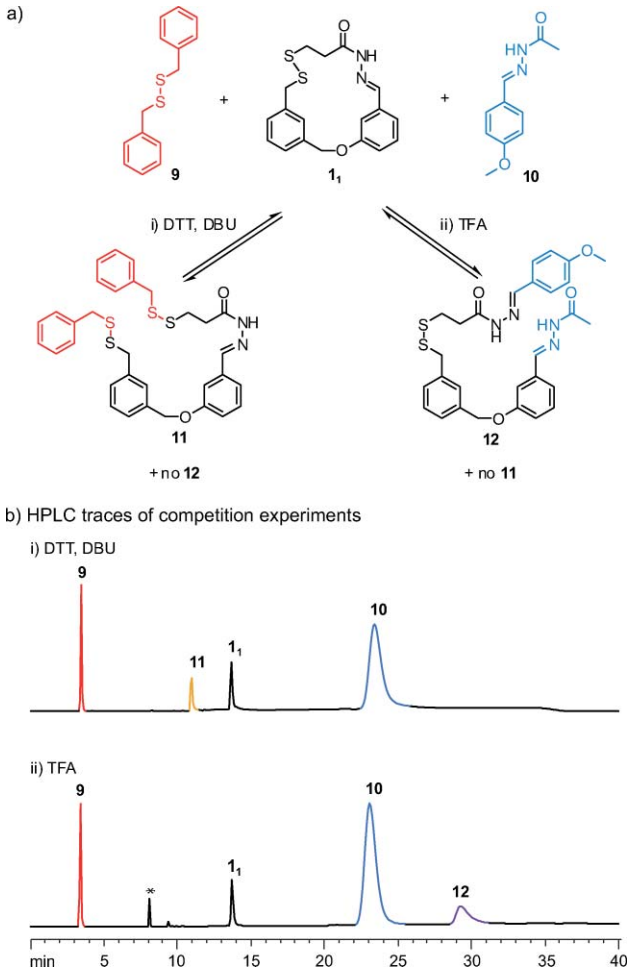


Fig. 3 Competition experiments in the presence of both scavengers **9** and **10** which demonstrated the mutually exclusive nature of conditions (i) and (ii) for disulfide and hydrazone exchange. (a) A mixture of macrocycle $\mathbf{1}_1$ (1 equiv.), disulfide scavenger **9** (5 equiv.) and hydrazone scavenger **10** (5 equiv.) was subjected to two sets of conditions in independent experiments: (i) basic conditions; DTT (0.1 equiv.), DBU (1.0 equiv.) in $CDCl_3$ (5 mL); (ii) acidic conditions; TFA (5 equiv.) in $CDCl_3$ (5 mL), 6 h. Initial concentration of $\mathbf{1}_1$ 12 M in both experiments (see experimental section for further details). (b) HPLC traces showing the outcome of the two competition experiments. (i) Equilibrium composition after treatment of a mixture of $\mathbf{1}_1$, **9** and **10** with DBU and DTT (see experimental section for details). (ii) Equilibrium composition after treatment with TFA (mixture was quenched with Et_3N prior to dilution for HPLC analysis). * Hydrolysis product of **10**, *p*-methoxybenzaldehyde. Note: The chromatographic method (see experimental section) does not account for the small amount of oligomers present, which are significantly more polar.

for HPLC analysis (after dilution: ~0.5 mM in $CHCl_3/CDCl_3$). When the diluted, unquenched solution (still containing 5 equiv. TFA) was not immediately injected for analysis, the still-dynamic system quickly responded to the dilution by a dramatic change in composition so that product **12** was no longer detected (see Fig. 4a). Fig. 4 provides a direct comparison of the HPLC traces corresponding to the unquenched (Fig. 4a) and quenched (Fig. 4b) samples.

These observations are explained by the fact that formation of **12** by reaction of macrocycle $\mathbf{1}_1$ with scavenger **10** is a bimolecular

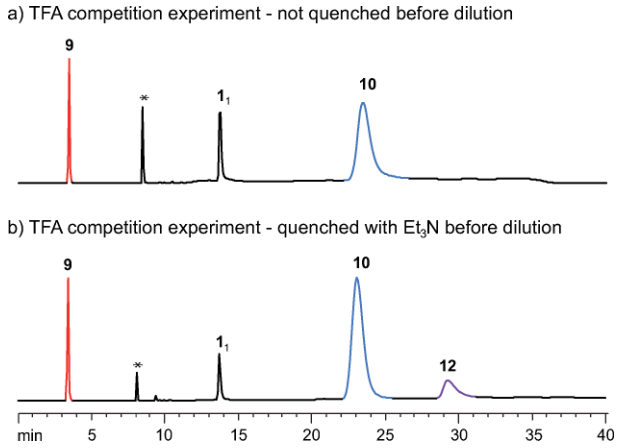


Fig. 4 Two HPLC traces obtained from one TFA-promoted hydrazone exchange competition experiment (see Fig. 3a and conditions (ii) specified in the caption of Fig. 3). (a) Sample prepared by dilution (~20-fold) and left standing for an hour prior to HPLC analysis. Since this sample was still dynamic after dilution, virtually all of **12** that had been present had been converted back to $\mathbf{1}_1$ and **10**. (b) Sample treated with excess Et_3N before dilution and left standing for an hour prior to HPLC analysis. Since addition of the base neutralised the acid, hydrazone exchange was switched off. Therefore this HPLC trace reflects the composition of the mixture before dilution. Note: The chromatographic method (see experimental section) does not account for the small amount of oligomers present, which are significantly more polar.

process and is therefore slower at lower concentrations. The reverse process of **12** into $\mathbf{1}_1$ and **10** is unimolecular and therefore occurs independent of concentration. This may also explain why, despite the solid state structure of macrocycle $\mathbf{1}_1$ showing evidence of ring strain, equilibration in the presence of scavengers under the conditions investigated (the second and third series of dynamic experiments) only gave minor amounts of the ring-opened products. The dynamic chemistry of the hydrazone-disulfide macrocyclic system is thus governed by a delicate balance of enthalpic and entropic effects. This offers the opportunity to manipulate relatively strained monomeric macrocycles under thermodynamic control without obtaining significant amounts of less strained ring-opened or oligomeric side products. These features were recently exploited to provide a mechanism by which a small molecule can "walk" processively down a molecular track.[5]

Conclusions

We have developed methodology for the synthesis of a novel macrocycle that contains both a disulfide and a hydrazone moiety and studied its dynamic chemistry. The solid state structure suggests that a certain amount of strain is caused by having several rigid elements within the framework of a 17-membered macrocycle. Sets of reaction conditions were established whereby the disulfide and hydrazone moieties can selectively undergo dynamic covalent exchange reactions in a mutually exclusive manner. Applications based on these systems are currently on-going in our laboratory.

Experimental

Materials and methods

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Dry CH_2Cl_2, $CHCl_3$ and THF were obtained by passing the solvent through an activated alumina column on a PureSolv™ solvent purification system (InnovativeTechnologies, Inc., MA). $CDCl_3$, DMSO-d_6, DMF, MeOH and benzene were purchased from Sigma-Aldrich. Compounds **2**,[14] **6**[15] and **10**[16] were prepared according to modified literature procedures. Compound **9** and 3-hydroxybenzaldehyde were purchased from Sigma Aldrich. Flash column chromatography was carried out using Kieselgel C60 (Merck, Germany) as the stationary phase. Analytical TLC was performed on precoated silica gel plates (0.25 mm thick, 60F254, Merck, Germany) and observed under UV light. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400 instrument, at a constant temperature of 298 K. Chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constants (J) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: m = multiplet, quint. = quintet, q = quartet, t = triplet, d = doublet, s = singlet, b = broad. Assignment of the ^{1}H NMR signals was accomplished by two-dimensional NMR spectroscopy (COSY, NOESY, HSQC, HMBC). See ESI for the labelling of the protons.† All melting points were determined using a Sanyo Gallenkamp apparatus and are uncorrected. ESI mass spectrometry was carried out by the mass spectrometry services at the University of Edinburgh and by the EPSRC National Centre at the University of Wales, Swansea. Analytical and preparative HPLC was performed on instruments of Gilson Inc., USA. For all shown chromatograms, a normal-phase column (Kromasil-Si, 250 × 4.6 mm) was used with gradient elution (1 mL min^{-1}, CH_2Cl_2–MeCN, 0 → 62.5% MeCN, UV detection @ 260 nm).

Procedures for competition experiments

(i) Dibenzyl disulfide **9** (72 mg, 0.29 mmol, 5.0 equiv.), benzoic acid [1-phenyl-meth-(*E*)-ylidene]-hydrazide **10** (56 mg, 0.29 mmol, 5.0 equiv.), DBU (8.8 mg, 58.6 µmol, 1.0 equiv.), DTT (1 mg, 6.5 µmol, 0.1 equiv.) and macrocycle $\mathbf{1_1}$ (21 mg, 58.6 µmol, 1.0 equiv.) were dissolved in $CDCl_3$ (5 mL, initial concentration of $\mathbf{1_1}$ 12 mM) and the mixture was stirred at room temperature until analytical HPLC indicated that the equilibrium composition was reached (24–48 h).

(ii) Dibenzyl disulfide **9** (72 mg, 0.29 mmol, 5.0 equiv.), benzoic acid [1-phenyl-meth-(*E*)-ylidene]-hydrazide **10** (56 mg, 0.29 mmol, 5.0 equiv.), TFA (33 mg, 22 µL, 0.29 mmol, 5.0 equiv.) and macrocycle $\mathbf{1_1}$ (21 mg, 58.6 µmol, 1.0 equiv.) were dissolved in $CDCl_3$ (5 mL, initial concentration of $\mathbf{1_1}$ 12 mM) and the mixture was stirred at room temperature until analytical HPLC indicated that the equilibrium composition was reached (6–12 h).

Syntheses

3-Chloromethylbenzyl alcohol (2). Synthesized according to a modified literature procedure.[14] At 5 °C, a solution of ethyl chloroformate (1.69 mL, 17.2 mmol, 1.0 equiv.) in THF (7 mL) was added dropwise to a solution of 3-(chloromethyl)-benzoic acid (3.02 g, 17.2 mmol, 1.0 equiv.) and Et_3N (2.39 mL, 17.2 mmol, 1.0 equiv.) in THF (30 mL). The reaction was allowed to proceed at 5 °C for 30 min before the Et_3NHCl precipitate was filtered off and washed with THF (40 mL). The combined THF phases were added over 30 min to a solution of $NaBH_4$ (1.66 g, 43 mmol, 2.5 equiv.) in H_2O (14 mL) at 10 °C. The mixture was stirred over night at room temperature and then acidified with 10% HCl (17 mL). The solution was extracted with Et_2O (3 × 50 mL), washed with a solution of 10% NaOH (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (SiO_2, hexane–EtOAc 8 : 2) of the residue gave **2** (2.50 g, 85%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 4H, H_b, H_c, H_d, H_e), 4.68 (s, 2H, H_f), 4.60 (s, 2H, H_a), 2.32 (bs, 1H, H_g); LRMS (EI): m/z = 156.1 [M]$^+$.

3-(3-(Hydroxymethyl)benzyloxy)benzaldehyde (3). Under N_2, 3-hydroxybenzaldehyde (3.87 g, 31.69 mmol, 1.0 equiv.) was dissolved in DMF (25 mL) and cooled to 0 °C. NaH (60% in mineral oil, 1.27 g, 31.75 mmol, 1.0 equiv.) was added and the mixture was stirred until all NaH was dissolved (temperature allowed to raise to room temperature). A solution of **2** (3.31 g, 21.14 mmol, 0.67 equiv.) in DMF (25 mL) was added dropwise. The reaction was stirred for 48 h at room temperature and monitored by TLC (silica gel, toluene–EtOAc 3 : 1). After TLC showed that no starting material remained, 1 M HCl (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1 M HCl (50 mL) H_2O (50 mL) and brine (50 mL), and dried over $MgSO_4$. Concentration under reduced pressure yielded a residue, which was purified by flash column chromatography (SiO_2, toluene–EtOAc 15 : 2) to give **3** (4.27 g, 83%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1H, H_a), 7.50–7.45 (m, 4H, H_{Ar}), 7.42–7.34 (m, 3H, H_{Ar}), 7.27–7.24 (m, 1H, H_{Ar}), 5.13 (s, 2H, H_f), 4.73 (s, 2H, H_k), 1.79 (bs, 1H, H_l); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.13 (d), 159.27 (s), 141.46 (s), 137.81 (s), 136.65 (s), 130.15 (d), 128.91 (d), 127.60 (d), 127.60 (d), 126.03 (d), 123.79 (d), 122.20 (d), 113.21 (d), 70.12 (t), 65.07 (t); HRMS (ESI): m/z = 260.1279 [M+NH$_4$]$^+$ (calcd. 260.1281 for $C_{15}H_{18}NO_3$).

3-(3-(Bromomethyl)benzyloxy)benzaldehyde (4). Under N_2, **3** (2.10 g, 8.67 mmol, 1.0 equiv.) was dissolved in benzene (25 mL). A solution of $SOBr_2$ (3.75 g, 1.40 mL, 18.05 mmol, 2.1 equiv.) in benzene (20 mL) was added dropwise at 0 °C. The reaction was monitored by TLC (SiO_2, toluene–EtOAc 3 : 1). Stirring was continued for 48 h at room temperature until TLC indicated that no starting materials remained. H_2O (25 mL) was added and the mixture was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with H_2O (50 mL), dried with brine (50 mL) and over $MgSO_4$ and concentrated under reduced pressure to yield a brownish oil. The residue was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2–EtOAc 15 : 1 : 1) to yield **4** (1.92 g, 73%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.98 (s, 1H, H_a), 7.51–7.45 (m, 4H, H_{Ar}), 7.39–7.37 (m, 3H, H_{Ar}), 7.27–7.24 (m, 1H, H_{Ar}), 5.12 (s, 2H, H_f), 4.52 (s, 2H, H_k); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.00 (d), 159.18 (s), 138.29 (s), 137.86 (s), 137.04 (s), 130.18 (d), 129.18 (d), 128.86 (d), 128.05 (d), 127.50 (d), 123.86 (d), 122.16 (d), 113.20 (d), 69.81 (t), 33.15 (t); HRMS (ESI): m/z = 322.0433 [M+NH$_4$]$^+$ (calcd. 322.0437 for $C_{15}H_{17}NO_2Br$).

Thioacetic acid *S*-[3-(3-formyl-phenoxymethyl)-benzyl] ester (5). **4** (1.81 g, 5.93 mmol, 1.0 equiv.) was dissolved in DMF (20 mL) and a solution of KSAc (1.36 g, 11.91 mmol, 2.0 equiv.) in DMF (20 mL) was added dropwise. The mixture was stirred over night at room temperature. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with 1 M HCl (20 mL), H_2O (20 mL), and brine (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure yielded **5** (1.70 g, 95%) as a brownish oil that did not require further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.98 (s, 1H, H_a), 7.50–7.44 (m, 3H, H_{Ar}), 7.37 (s, 1H, H_{Ar}), 7.34–7.31 (m, 2H, H_{Ar}), 7.29–7.24 (m, 2H, H_{Ar}), 5.09 (s, 2H, H_f), 4.14 (s, 2H, H_k), 2.36 (s, 3H, H_l); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.02 (s), 192.09 (d), 159.22 (s), 138.22 (s), 137.81 (s), 136.75 (s), 130.16 (d), 129.01 (d), 128.70 (d), 127.97 (d), 126.50 (d), 123.73 (d), 122.15 (d), 113.27 (d), 69.95 (t), 33.27 (t), 30.36 (q); HRMS (ESI): m/z = 318.1157 $[M+NH_4]^+$ (calcd. 318.1158 for $C_{17}H_{20}NO_3S$).

3-Mercaptopropanehydrazide (6). Synthesized according to a modified literature procedure.[15] Methyl 3-mercaptopropionate (10 g, 83 mmol, 1.0 equiv.) was added dropwise to a solution of hydrazine monohydrate (10 g, 200 mmol, 2.4 equiv.) in MeOH (30 mL). The reaction mixture was stirred over night at room temperature. Evaporation of the solvent, followed by flash column chromatography (SiO_2, Et_2O–MeOH 8 : 2) gave **6** (4.99 g, 50%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (bs, 1H, H_d), 3.93 (bs, 2H, H_c), 2.84 (dt, J = 8.4 Hz, 6.4 Hz, 2H, H_b), 2.50 (t, J = 6.7 Hz, 2H, H_c), 1.61 (t, J = 8.4 Hz, 1H, H_a).

Thioacetic acid *S*-(3-{3-[(3-mercapto-propionyl)-hydrazono-methyl]-phenoxymethyl}-benzyl) ester (7). **5** (1.33 g, 4.38 mmol, 1.0 equiv.) was dissolved in MeOH (25 mL) and 5 drops of acetic acid were added. A solution of **6** (673 mg, 5.60 mmol, 1.3 equiv.) in MeOH (15 mL) was added dropwise after which the mixture was stirred for 3 h at room temperature. The reaction was monitored by TLC (SiO_2, cyclohexane/EtOAc 5 : 2). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 5 : 2 → 3 : 2) to yield a mixture of thioester **7** and dithiol **8** in a ratio of 85 : 15 (1.52 g, 88%). *E*/Z ratio of the hydrazone was approximately 9 : 1. Major *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1H, H_p), 7.72 (s, 1H, H_a), 7.34 (s, 1H, H_{Ar}), 7.34–7.27 (m, 5H, H_{Ar}), 7.21 (d, J = 7.6 Hz, 1H, H_{Ar}), 7.02 (ddd, J = 8.2, 2.7, 0.8 Hz, 1H, H_{Ar}), 5.07 (s, 2H, H_f), 4.14 (s, 2H, H_k), 3.12 (t, J = 6.9 Hz, 2H, H_o), 2.91 (dt, J = 8.3, 6.9 Hz, 2H, H_n), 2.36 (s, 3H, H_l), 1.74 (t, J = 8.3 Hz, 1H, H_m); some characteristic signals of the minor *Z*-isomer; 8.70 (s, 1H, H_p), 8.12 (s, 1H, H_a), 5.06 (s, 2H, H_f), 2.64 (t, J = 6.6 Hz, 2H, H_o); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.04 (s), 173.83 (s), 159.02 (s), 143.85 (d), 138.14 (s), 137.10 (s), 135.04 (s), 129.88 (d), 128.99 (d), 128.61 (d), 127.95 (d), 126.50 (d), 120.58 (d), 117.01 (d), 112.66 (d), 69.96 (t), 36.95 (t), 33.32 (t), 30.35 (q), 19.47 (t); HRMS (ESI): m/z = 403.1144 $[M+H]^+$ (calcd. 403.1145 for $C_{20}H_{23}N_2O_3S_2$).

3-Mercapto-propionic acid [1-[3-(3-mercaptomethyl-benzyloxy)-phenyl]-meth-(*E*)-ylidene]-hydrazide (8). Under N_2, a mixture of starting material **7** and the product **8** (85 : 15, 1.50 g, 3.80 mmol, 1.0 equiv.) was dissolved in MeOH (25 mL). A solution of NaOMe (246 mg, 4.55 mmol, 1.2 equiv.) in MeOH (15 mL) was added. After 2 h NH_4Cl, (satd., 20 mL) was added and the mixture was stirred for another 15 min. The mixture was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with H_2O (2 × 50 mL) and brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a 15 : 1 mixture of **8** and $\mathbf{1_1}$ (1.07 g, 78%) as a thick transparent oil. The dithiol **8** was found in an *E*/*Z* ratio of about 9 : 1. Major *E*-isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1H, H_n), 7.72 (s, 1H, H_a), 7.43 (s, 1H, H_{Ar}), 7.38–7.30 (m, 5H, H_{Ar}), 7.22 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.02 (ddd, J = 8.2, 2.6, 0.8 Hz, 1H, H_{Ar}), 5.10 (s, 2H, H_f), 3.77 (d, J = 7.6 Hz, 2H, H_k), 3.12 (t, J = 6.9 Hz, 2H, H_o), 2.91 (dt, J = 8.2, 6.9 Hz, 2H, H_n), 1.79 (t, J = 7.6 Hz, 1H, H_l), 1.74 (t, J = 8.2 Hz, 1H_m); characteristic signals of the minor *Z*-isomer: 8.71 (s, 1H, H_n), 8.12 (s, 1H, H_a), 5.08 (s, 2H, H_f), 2.64 (t, J = 6.5 Hz, 2H, H_m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.10 (s), 159.01 (s), 144.08 (d), 141.61 (s), 137.14 (s), 135.10 (s), 129.90 (d), 129.04 (d), 127.86 (d), 127.20 (d), 126.27 (d), 120.64 (d), 116.99 (d), 112.60 (d), 69.94 (t), 36.94 (t), 28.89 (t), 19.52 (t); HRMS (ESI): m/z = 378.1300 $[M+NH_4]^+$ (calcd. 378.1304 for $C_{18}H_{24}N_3O_2S_2$).

2-Oxa-10,11-dithia-15,16-diazatricyclo[16.3.1.1^{4,8}] tricosa-1(22),4,6,8(23),16,18,20-heptaen-14-one ($\mathbf{1_1}$). Under N_2, a mixture of dithiol **8** and disulfide $\mathbf{1_1}$ (15 : 1, 360 mg, 1.00 mmol, 1.0 equiv.) was dissolved in MeOH (100 mL) and CH_2Cl_2 (100 mL). A solution of KI (51 mg, 0.303 mmol, 0.3 equiv.) in MeOH (~5 mL) was added and subsequently, at 0 °C, a solution of I_2 (267 mg, 1.05 mmol, 1.05 equiv.) in MeOH (~ 25 mL) was added dropwise until the brown colour persisted. Na_2SO_3 was added and, when decolourisation was complete, stirring was continued for 15 min. H_2O (100 mL) and CH_2Cl_2 (100 mL) were added and the H_2O layer was extracted another time with CH_2Cl_2 (100 mL). The combined organic layers were washed with H_2O (100 mL) and with brine (100 mL) and dried ($MgSO_4$). Removal of the solvents under reduced pressure and purification by flash column chromatography (SiO_2, $CHCl_3$–EtOAc 3 : 1) yielded pure $\mathbf{1_1}$ (200 mg, 56%) as a colourless solid. M.p. 188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.48 (s, 1H, H_n), 7.66 (s, 1H, H_a), 7.48 (s, 1H, H_j), 7.39 (dd, J = 2.6, 1.5 Hz, 1H, H_e), 7.30–7.28 (m, 3H, H_c, H_g, H_h), 7.19 (ddd, J = 6.7, 1.5, 0.9 Hz, 1H, H_i), 7.06 (ddd, J = 8.4, 2.6, 0.9 Hz, 1H, H_d), 6.89 (d, J = 7.4 Hz, 1H, H_b), 5.28 (s, 2H, H_f), 3.89 (s, 2H, H_k), 3.14 (dd, J = 7.7, 7.1 Hz, 2H, H_m), 2.92 (dd, J = 7.7, 7.1 Hz, 2H, H_l); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.37 (s), 157.95 (s), 142.07 (d), 137.35 (s), 137.05 (s), 135.36 (s), 129.91 (d), 129.68 (d), 129.00 (d), 128.19 (d), 126.10 (d), 122.24 (d), 119.69 (d), 107.31 (d), 68.81 (t), 41.08 (t), 31.14 (t), 30.37 (t); ε (260 nm, CH_2Cl_2) = 7872.5 dm^3 mol^{-1} cm^{-1}; HRMS (ESI): m/z = 359.0882 $[M+H]^+$ (calcd. 359.0882 for $C_{18}H_{19}N_2O_2S_2$).

Benzoic acid [1-phenyl-meth-(*E*)-ylidene]-hydrazide (10). Synthesized according to a modified literature procedure.[16] A mixture of *p*-anisaldehyde (2.0 g, 14.7 mmol, 1.0 equiv.) and acethydrazide (1.21 g, 14.7 mmol, 1.0 equiv.) in EtOH (100 mL) was stirred at room temperature for 3 h. Filtration of the precipitate and recrystallisation from EtOH gave **10** (1.84 g, 65%) as a colourless, crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (bs, 1H, H_e), 7.75 (sb, 1H, H_d), 7.61 (d, J = 8.8 Hz, 2H, H_c), 6.92 (d, J = 8.8 Hz, 2H, H_b), 3.85 (s, 3H, H_a), 2.37 (s, 3H, H_f); ε (260 nm, CH_2Cl_2) = 6353.5 dm^3 mol^{-1} cm^{-1}.

3-Benzyldisulfanyl-propionic acid [1-[3-(3-benzyl disulfanyl-methyl-benzyloxy)-phenyl]-meth-(*E*)-ylidene]-hydrazide (11).

Dibenzyl disulfide **9** (72 mg, 0.29 mmol, 5.0 equiv.), DBU (45 mg, 0.30 mmol, 5.1 equiv.), DTT (1 mg, 6.48 μmol, 0.1 equiv.) and macrocycle $\mathbf{1_1}$ (21 mg, 58.6 μmol, 1.0 equiv.) were dissolved in $CDCl_3$ (5 mL, initial concentration of $\mathbf{1_1}$ 12 mM) and the mixture was stirred for 48 h. The reaction mixture was directly subjected to flash column chromatography (SiO_2, $CHCl_3$–EtOAc 5 : 1) to yield **11** (10 mg, 28%) as an oil. Signals for the minor *Z*-isomer were also observed (<10%). Major *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1H, H_g), 7.66 (s, 1H, H_h), 7.36–7.16 (m, 17H, H_{a-c}, H_i, H_j, H_l, H_{n-q}, H_{t-v}), 7.03 (ddd, J = 8.2, 1.9, 0.7 Hz, 1H, H_k), 5.09 (s, 2H, H_m), 3.93 (s, 2H, H_r), 3.59 (s, 2H, H_s or H_d), 3.57 (s, 2H, H_s or H_d), 3.08 (t, J = 7.3 Hz, 2H, H_f), 2.82 (t, J = 7.3 Hz, 2H, H_e); characteristic signals of minor *Z*-isomer: 8.48 (s, 1H, H_g), 8.05 (s, 1H, H_h), 3.92 (s, 2H, H_r), 2.72 (t, J = 7.0 Hz, 2H, H_e), 2.50 (t, J = 7.0 Hz, 2H, H_f);^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.48 (s), 158.99 (s), 143.39 (d), 137.88 (s), 137.31 (s), 137.22 (s), 136.98 (s), 134.95 (s), 129.91 (d), 129.43 (d), 129.32 (d), 129.19 (d), 128.80 (d), 128.57 (d), 128.51 (d), 128.48 (d), 127.50 (d), 127.47 (d), 126.56 (d), 120.58 (d), 117.81 (d), 112.55 (d), 69.87 (t), 43.57 (t), 43.28 (t), 43.03 (t), 32.98 (t), 32.79 (t); ε (260 nm, CH_2Cl_2) = 9677.9 dm^3 mol^{-1} cm^{-1}; HRMS (ESI): m/z = 626.11647 [M+Na–H]$^+$ (calcd. 626.11606 for $C_{32}H_{31}N_2O_2S_4Na$).

3-{3-[3-(Acetyl-hydrazonomethyl)-phenoxymethyl]-benzyl disulfanyl}-propionic acid [1-(4-methoxy-phenyl)-meth-(*E*)-ylidene]-hydrazide (12). Hydrazide **10** (67 mg, 0.35 mmol, 5.0 equiv.) and macrocycle $\mathbf{1_1}$ (25 mg, 69.7 μmol, 1.0 equiv.) were dissolved/suspended in $CDCl_3$ (6 mL, initial concentration of $\mathbf{1_1}$ 12 mM). TFA-d_1 (40 mg, 26 μL, 0.35 mmol, 5.0 equiv.) was added and the mixture was stirred for 12 h. The reaction was monitored by ^{1}H NMR. During the reaction, the mixture slowly turned transparent yellowish. The reaction mixture was directly subjected to flash column chromatography (SiO_2, $CHCl_3$–EtOAc 1 : 1 → 1 : 3) to give **12** (10 mg, 26%) as an oil. Signals for the minor *Z*-isomers were also observed (<10%). Major *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.39 (s, 1H, H_e or H_s), 10.13 (s, 1H, H_e or H_s), 7.77 (s, 1H, H_d or H_r), 7.75 (s, 1H, H_d or H_r), 7.60 (d, J = 8.8 Hz, 2H, H_c), 7.41 (s, 1H, H_l), 7.32–7.26 (m, 5H, H_i, H_j, H_k, H_o, H_q), 7.12 (d, J = 1.7 Hz, 1H, H_p), 6.98 (ddd, J = 6.7, 2.7, 2.4 Hz, 1H, H_n), 6.90 (d, J = 8.8 Hz, 2H, H_b), 5.10 (s, 2H, H_m), 3.93 (s, 2H, H_h), 3.83 (s, 3H, H_a), 3.10 (dd, J = 7.1, 6.9 Hz, 2H, H_f), 2.89 (dd, J = 7.1, 6.9 Hz, 2H, H_g), 2.35 (s, 3H, H_t); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.26 (s), 174.02 (s), 161.27 (s), 158.80 (s), 144.22 (d), 144.15 (d), 137.93 (s), 137.18 (s), 135.19 (s), 129.81 (d), 129.03 (d), 128.97 (d), 128.75 (d), 128.21 (d), 126.42 (s), 126.37 (d), 119.37 (d), 117.46 (d), 114.22 (d), 113.39 (d), 69.85 (t), 55.38 (q), 43.22 (t), 34.30 (t), 33.06 (t), 20.32 (q); ε (260 nm, CH_2Cl_2) = 14079.0 dm^3 mol^{-1} cm^{-1}; HRMS (ESI): m/z = 551.1777 [M+H]$^+$ (calcd. 551.1781 for $C_{28}H_{31}N_4O_4S_2$).

Crystallographic data

$\mathbf{1_1}$. Empirical formula $C_{18}H_{18}N_2O_2S_2$, Formula weight 358.46, Temperature 93(2) K, Wavelength 0.71073 Å, Crystal system Monoclinic, Space group $P2_1/n$, Unit cell dimensions a = 6.886(2) Å α = 90°, b = 9.252(3) Å, β = 96.481(5)°, c = 26.755(8) Å, γ = 90°, Volume 1693.5(10) Å3 Z 4, Density (calculated) 1.406 Mg/m3, Absorption coefficient 0.327 mm^{-1}, F(000) 752, Crystal size 0.0800 × 0.0800 × 0.0800 mm3,Theta range for data collection 2.33 to 25.33°, Index ranges −8 < h < 8, −11 < k < 11, −32 < l < 29, Reflections collected 14385, Independent reflections 2984 [R(int) = 0.0813], Completeness to theta = 25.00° 96.6%, Absorption correction multiscan, max. and min. transmission 1.0000 and 0.9163, Refinement method full-matrix least-squares on F2, Data/restraints/parameters 2984/1/223, Goodness-of-fit on F2 0.949, Final R indices [$I > 2\sigma(I)$] R_1 = 0.0517, wR_2 = 0.1273, R indices (all data) R_1 = 0.0553, wR_2 = 0.1344, Extinction coefficient 0.050(9), Largest diff. peak and hole 0.311 and −0.283 e.Å^{-3}.

Acknowledgements

We thank the EPSRC National Mass Spectrometry Service Centre (Swansea, UK) for high resolution mass spectrometry. This research was funded through the European Research Council Advanced Grant *WalkingMols* and the EPSRC. D.A.L. is an EPSRC Senior Research Fellow and holds a Royal Society-Wolfson Research Merit Award.

Notes and references

1 (*a*) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2002, **41**, 898; (*b*) J.-M. Lehn, *Chem. Soc. Rev.*, 2007, **36**, 151; (*c*) J.-M. Lehn and A. V. Eliseev, *Science*, 2001, **291**, 2331; (*d*) J.-M. Lehn, *Chem.–Eur. J.*, 1999, **5**, 2455; (*e*) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652.

2 (*a*) R. F. Ludlow and S. Otto, *Chem. Soc. Rev.*, 2008, **37**, 101; (*b*) J. R. Nitschke, *Nature*, 2009, **462**, 736.

3 We use the term 'constitutionally dynamic' here to include both reversible metal coordination and dynamic covalent processes (see reference 1b).

4 (*a*) V. Goral, M. I. Nelen, A. V. Eliseev and J.-M. Lehn, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 1347; (*b*) J. Leclaire, L. Vial, S. Otto and J. K. M. Sanders, *Chem. Commun.*, 2005, 1959; (*c*) D. Schultz and J. R. Nitschke, *Angew. Chem., Int. Ed.*, 2006, **45**, 2453; (*d*) R. J. Sarma, S. Otto and J. R. Nitschke, *Chem.–Eur. J.*, 2007, **13**, 9542; (*e*) N. Christinat, R. Scopelliti and K. Severin, *Angew. Chem., Int. Ed.*, 2008, **47**, 1848; (*f*) M. Hutin, G. Bernardinelli and J. R. Nitschke, *Chem.–Eur. J.*, 2008, **14**, 4585; (*g*) R. J. Sarma and J. R. Nitschke, *Angew. Chem., Int. Ed.*, 2008, **47**, 377; (*h*) V. E. Campbell, X. de Hatten, N. Delsuc, B. Kauffmann, I. Huc and J. R. Nitschke, *Chem.–Eur. J.*, 2009, **15**, 6138; (*i*) P. Mal and J. R. Nitschke, *Chem. Commun.*, 2010, **46**, 2417.

5 M. von Delius, E. M. Geertsema and D. A. Leigh, *Nat. Chem.*, 2010, **2**, 96.

6 E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2007, **46**, 72.

7 The term double-level (dynamic covalent) system denotes a system whose building blocks are interconnected by two different types of exchange processes (see, for example, references 4a,4b, 8a and 8b).

8 (*a*) A. G. Orrillo, A. M. Escalante and R. L. E. Furlan, *Chem. Commun.*, 2008, 5298; (*b*) Z. Rodriguez-Docampo and S. Otto, *Chem. Commun.*, 2008, 5301.

9 $\mathbf{1_1}$ is the smallest cyclic oligomer of type $\mathbf{1_n}$, where **1** denotes the repeat structure and the subscript **n** denotes the numbers of repeat units in the molecule.

10 An alternative strategy to introduce the disulfide linkage prior to ring-closure by hydrazone condensation failed, as various methodologies for the synthesis of unsymmetric disulfide bonds [(*a*) R. Hunter, M. Caira and N. Stellenboom, *J. Org. Chem.*, 2006, **71**, 8268; (*b*) S. Antoniow and D. Witt, *Synthesis*, 363; (*c*) J. Kowalczyk, P. Barski, D. Witt and B. A. Grzybowski, *Langmuir*, 2007, **23**, 2318] proved low yielding or unsuccessful in our hands.

11 T. J. Kucharski, Z. Huang, Q.-Z. Yang, Y. Tian, N. C. Rubin, C. D. Concepcion and R. Boulatov, *Angew. Chem., Int. Ed.*, 2009, **48**, 7040.

12 (*a*) G. R. L. Cousins, S.-A. Poulsen and J. K. M. Sanders, *Chem. Commun.*, 1999, 1575; (*b*) A. T. ten Cate, P. Y. W. Dankers, R. P. Sijbesma and E. W. Meijer, *J. Org. Chem.*, 2005, **70**, 5799; (*c*) A. L. Kieran, A. D. Bond, A. M. Belenguer and J. K. M. Sanders, *Chem. Commun.*, 2003, 2674.
13 Cyclooligomerisation of $\mathbf{1}_1$ *via* disulfide exchange is possible either in a head-to-head (two benzylic disuflide fragments), tail-to-tail (two thioethyl hydrazone fragments) or head-to-tail (one of each) fashion, while hydrazone exchange alone can only give rise to head-to-tail oligomers.
14 N. Iqbal, C.-A. McEwen and E. E. Knaus, *Drug Dev. Res.*, 2000, **51**, 177.
15 M. D. Costioli, D. Berdat, R. Freitag, X. André and A. H. E. Müller, *Macromolecules*, 2005, **38**, 3630.
16 J. R. Dimmock, S. C. Vashishtha and J. P. Stables, *Eur. J. Med. Chem.*, 2000, **35**, 241.

