Dynamic supramolecular complexation by shapeshifting organic molecules†

Alexander R. Lippert, Vasken L. Keleshian and Jeffrey W. Bode*

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The synthesis of bisporphyrin bullvalene 1 enabled explorations of its supramolecular complexation with C_{60}, revealing a dynamic network of interconverting complexes.

Dynamic combinatorial chemistry[1] exploits reversible chemical reactions to create molecular systems capable of responding and adapting to their environment. A long-standing goal of this field is the development of robust, general approaches to the rapid discovery of systems with designed properties, such as the ability to act as receptors[2] or sensors.[3] Despite impressive progress, there remains a need for the identification of rapidly reversible, yet chemically robust, reactions to generate dynamic diversity. In seeking to address this, we hypothesized that mounting key recognition elements onto a dynamic bullvalene[4] scaffold would result in a shapeshifting molecule that would act as a dynamic library. Strain-assisted Cope rearrangements allow bullvalenes to rapidly interconvert between millions of degenerate valence isomers, a property that can be exploited to generate structural diversity by introducing substitution on the bullvalene carbons. For example, attaching just two identical substituents results in a dynamic library of 15 distinct isomers (Fig. 1).

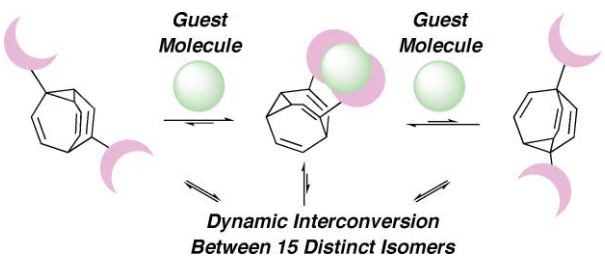
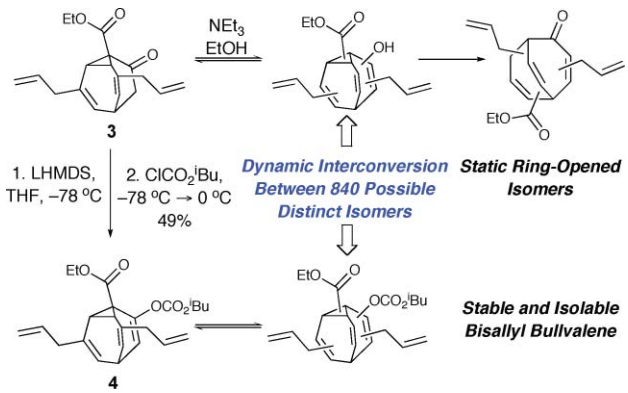


Fig. 1 Disubstituted bullvalenes act as a single component dynamic library of distinct configurational isomers.

We now demonstrate the feasibility of this approach to dynamic host discovery. As a proof of principle, we selected the high affinity π–π interactions of porphyrin with C_{60}[5] to establish the binding ability of a synthetic, shapeshifting molecular system. Our preliminary investigations of the interaction of this dynamic ensemble with C_{60} reveal that it rapidly adapts into a network of multiple interconverting supramolecular complexes bound with C_{60}.

We have previously synthesized oligosubstituted bullvalone **3**,[6] which exhibited constitutional isomerism mediated through a hydroxy bullvalene enol form. Initial efforts to utilize the adaptive properties of porphyrin-functionalized bullvalones as single-component dynamic combinatorial libraries were hindered by the decomposition of certain hydroxyl cyclopropane isomers, resulting in the gradual accumulation of static structures (Scheme 1). In order to improve the robustness of the system, the enol form was trapped as the enol carbonate to produce the tetra-substituted bisallyl bullvalene **4**. Eliminating the donating capability of the hydroxyl group provided a chemically stable scaffold for more advanced functionalization. Variable-temperature NMR and exchange correlation spectroscopy (2D-EXSY)[7] confirmed the dynamic properties and thermal stability of this unique molecule (see ESI†).



Scheme 1 Synthesis of oligosubstituted bullvalene carbonate **4** as a robust, dynamic, and addressable shapeshifting molecule.

We selected olefin cross-metathesis as a convergent strategy for the introduction of new functionalities into the dynamic bullvalene core, thereby minimizing complications involved in the purification of molecules capable of spontaneous shape-changing rearrangements. Acrylamide porphyrin **6** was prepared from the known amino porphyrin **5**.[8] Despite the fact that **4** is a dynamic, interconverting mixture of 840 possible constitutional isomers, we successfully effected chemoselective cross-metathesis of the acrylamide porphyrin with bisallyl bullvalene **4**, and purified the resulting dynamic mixture, in ~20% yield. As a non-dynamic control, bisporphyrin bullvalone **2** was synthesized in an analogous manner (Scheme 2).

With a route to fluxional bisporphyrin bullvalene **1** in hand, we investigated its binding properties in comparison to the static bisporphyrin bullvalone **2**. Since we expected that the static control **2** would also have some affinity towards C_{60}, this comparison allowed us to interrogate whether single or multiple complexes would be formed upon the addition of C_{60} to dynamic system **1**. Likewise, we posed the following question: would the ability of **1** to change its shape allow it to adapt to more tightly bind a guest C_{60} molecule, or would the binding be weaker due to a population of weakly binding isomers in the dynamic equilibrium?

Department of Chemistry, University of Pennsylvania, Philadelphia, PA, USA 19104-6323. E-mail: bode@sas.upenn.edu

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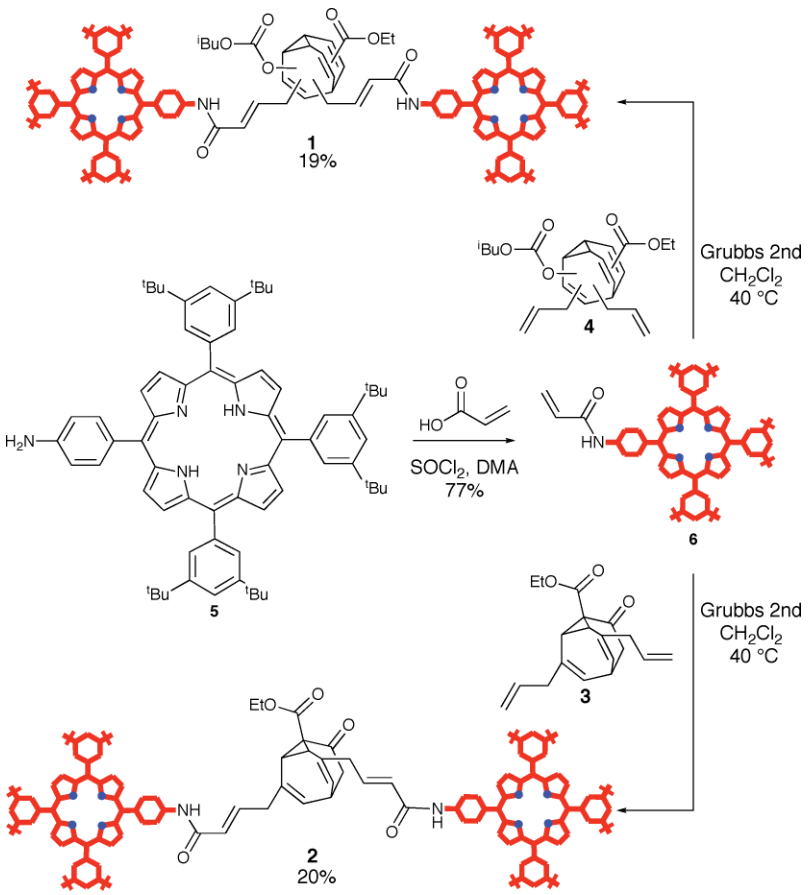

Scheme 2 Synthesis of bisporphyrin bullvalene **1** and bisporphyrin bullvalone **2**.

The dynamic nature of **1** presents considerable, but not insurmountable, challenges to the analysis of its supramolecular complexes. We began by establishing analytical methods for spectrophotometric titrations on the simpler, static bisporphyrin bullvalone **2** (Fig. 2a). Differential absorbance plots revealed two general maxima. The negative peak at 421 nm, assigned to the free porphyrin, decreases upon the addition of C_{60}, while the peak at 434 nm, corresponding to the complexed porphyrin, increases upon the addition of C_{60}. An isosbestic point at 427 nm and Job's plots (Fig. S2) indicated the formation of a single 1 : 1 complex, and a binding constant of 2700 ± 120 M^{-1} was calculated from the change in absorbance at 421 nm (Table 1, entry 1).

When the same experiments were performed with dynamic bisporphyrin bullvalene **1**, far more complex results were obtained.

Table 1 Binding constants calculated for bisporphyrin bullvalene **1** and bisporphyrin bullvalone **2**

Entry	No.	Peak	Temp	K_b/M^{-1}	Method
1	**2**	—	25 °C	2700 ± 120	UV
2	**2**	b	25 °C	2800 ± 210	NMR
3	**1**	d	25 °C	3030 ± 430^a	NMR
4	**1**	e	25 °C	6770 ± 1800^a	NMR
5	**2**	a	90 °C	570 ± 65	NMR
6	**1**	c	90 °C	920 ± 100	NMR

[a] Minimum binding constants. See text and ref. 11 for details.

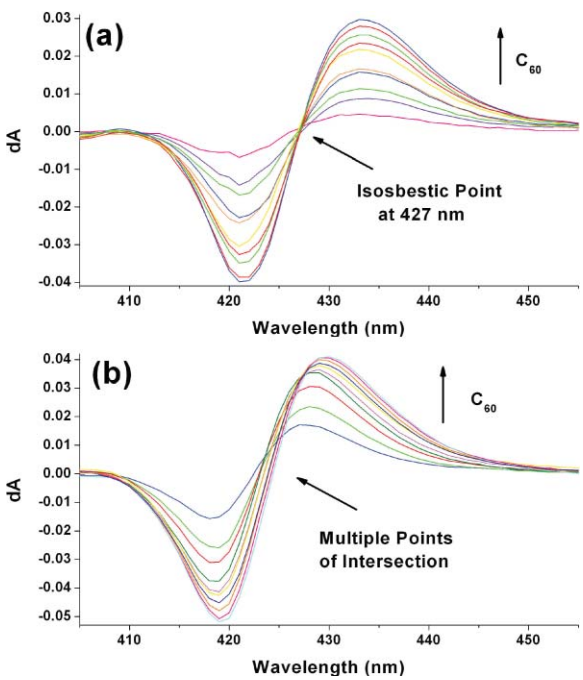

Fig. 2 Differential absorbance plots at increasing concentrations of C_{60}. (a) 2.9 μM Bisporphyrin bullvalone **2** and 2–20 equiv C_{60} in toluene. (b) 2.1 μM Bisporphyrin bullvalene **1** and 1–10 equiv of C_{60} in toluene.

While the differential absorbance plots still display the general maxima for free and complexed bisporphyrin, multiple points of intersection were indicative of multiple spectroscopically unique species (Fig. 2b).[9] Calculation of the binding constant as well as Job's plots gave variable results dependent on the wavelength used, a further indication of multiple complexes. The presence of multiple binding complexes hampered our ability to use standard models to calculate binding constants from the spectrophotometric titration data.[9] Interestingly, when greater than 20 equivalents of C_{60} were added, the differential absorbance plots began to show a single isosbestic point, possibly due to the predominance of a single isomeric species at higher equivalents of C_{60} (Fig. S3). Although Job's plots proved to be inconclusive, we were eventually able to confirm the stoichiometry of the complexes of **1** and C_{60} due to the stability of these complexes to supercritical fluid CO_2 chromatography, which allowed us to analytically separate the bound and unbound species (Fig. S11). Based on the relative extinctions for the porphyrin and C_{60} in the diode array spectrum of the bound species, we confirmed a 1 : 1 stoichiometry of C_{60}–**1**.

In order to attain greater insight into the number and nature of these bisporphyrin bullvalene–C_{60} complexes, we performed a series of NMR studies (Fig. 3). It has been demonstrated that the internal N–H protons of the porphyrin, which are shifted upfield to around –2 ppm due to the ring current effect of the aromatic porphyrin system, provide a convenient assay of the binding event.[5b] Upon addition of C_{60} to the static bisporphyrin bullvalone **2**, a single peak was observed in the region near –2.2 ppm for a single porphyrin–C_{60} complex in fast exchange with the unbound bisporphyrin (peak b, Fig. 3a). For the bisporphyrin bullvalene **1**, however, there appeared to be two main peaks present in the region of the bound species (peaks d and e, Fig. 3b). Each of these peaks arise from the fast exchange between the bound and unbound species of different valence isomers of **1**. The coalescence of these peaks at higher temperatures (peak c, Fig. 3b) indicates that the different valence isomers are in the slow to intermediate exchange regime at 25 °C. ^{1}H NMR titrations[10] were performed on the bisporphyrin bullvalone **2** (peak b, Fig. 3a), as well as on the two major observed complexes of bisporphyrin bullvalene **1** (peaks d and e, Fig. 3b). In order to get a direct comparison of the static bisporphyrin bullvalone **2** to the dynamic bisporphyrin bullvalene **1**, ^{1}H NMR titrations were also performed at 90 °C. At this temperature, the two peaks for the bound complexes are coalesced (peak c, Fig. 3b) and an average binding constant was estimated. The results are reported in Table 1.

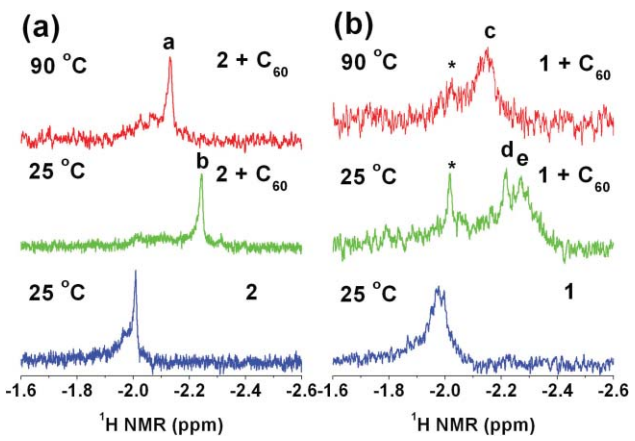

Fig. 3 ^{1}H NMR spectra of (a) 500 μM **2** and 3 equiv C_{60} in $C_6D_5CD_3$ at 90 °C and 25 °C and (b) 233 μM **1** and 3 equiv C_{60} in $C_6D_5CD_3$ at 90 °C and 25 °C. The bottom traces are **1** and **2** with no C_{60} added. * indicates residual acrylamide porphyrin **6**.

The binding constants determined by ^{1}H NMR titrations for bisporphyrin bullvalone **2** at 25 °C were in good agreement with the values obtained from the spectrophotometric titrations (entries 1 and 2). The binding constant at 90 °C for bisporphyrin bullvalone **2** was calculated to be 570 ± 65 M^{-1} (entry 5). In comparison, the value calculated for the coalesced peak of the complexes of bisporphyrin bullvalene **1** was 920 ± 100 M^{-1} (entry 6), a measurably higher affinity than that calculated for bisporphyrin bullvalone **2**. At 25 °C, two peaks can be observed in the region of the bound complexes for bisporphyrin bullvalene **1**. These two resolved resonances indicate that at least two structurally distinct valence isomers are binding to C_{60} in solution. By carefully analyzing the change in chemical shifts of peaks d and e upon addition of C_{60}, we can obtain minimum binding affinities for each observed binding isomer.[11] For the more downfield peak (peak d, entry 3), a minimum binding constant of 3030 ± 430 M^{-1}, similar to that for the bisporphyrin bullvalone **2**, was determined. For the upfield peak (peak e, entry 4), however, the minimum calculated binding constant was found to be 6770 ± 1800 M^{-1}; more than twice as strong as bisporphyrin bullvalone **2**.

These results indicate that while the static bisporphyrin bullvalone **2** forms a single complex with C_{60}, the shapeshifting bisporphyrin bullvalene **1** forms a network of two or more interconverting complexes. Our binding studies indicate that the observed bisporphyrin bullvalene complexes bind at least as well, if not better, than static bisporphyrin bullvalone **2**. These results could be explained if the addition of C_{60} shifts the isomeric equilibrium of the fluxional bisporphyrin bullvalene **1** towards isomers that more tightly bind C_{60}. Another explanation would be that the isomeric distribution in the absence of C_{60} coincidentally favors isomers that more tightly bind C_{60} and there is no significant shift in the isomeric distribution. The appearance of a single isosbestic point in the differential absorbance plots at saturating equivalents of C_{60} (Fig. S3), as well as an apparent increase in the peak integrations of the more tightly bound complex during the ^{1}H NMR titrations (Fig. S7) support the former explanation, that the isomeric equilibrium is indeed shifting. While further experimentation and characterization is needed to identify the exact structure of the isomers involved in the binding,[12] this data demonstrates the feasibility of a self-contained, dynamic combinatorial library to spontaneously discover high affinity binding complexes when challenged with a suitable guest.

In conclusion, we have synthesized a shapeshifting bisporphyrin bullvalene **1**, thereby establishing a versatile route to elaborately functionalized bullvalenes that adapt their shape to bind guest molecules. Our evidence supports the presence of a network of two or more interconverting 1 : 1 complexes that bind more strongly than a nondynamic control. These studies demonstrate the potential of structurally adaptive organic molecules to respond to their environment and adopt structures with favorable supramolecular interactions.

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11 These binding constants are minimum values based on the assumption that each isomer represents 100% of the isomeric distribution. In actuality, the population of each binding isomer is a difficult-to-measure fraction of this value, which would lead to higher calculated affinities. For example, if the isomer giving rise to peak e in Fig. 3b represented 50% of the isomeric distribution, this would lead to a $K_b = 13550 \pm 3637\ M^{-1}$. See the ESI for further details.

12 See the ESI, Section F, for examples of isomers of bisporphyrin bullvalene **1** that might be predicted to have a higher binding affinity for C_{60} than bisporphyrin bullvalone **2**.

