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Probing the Dynamic Covalent Chemistry Behavior of Nitrogen-Centered Di and Tri–Urazole Radicals

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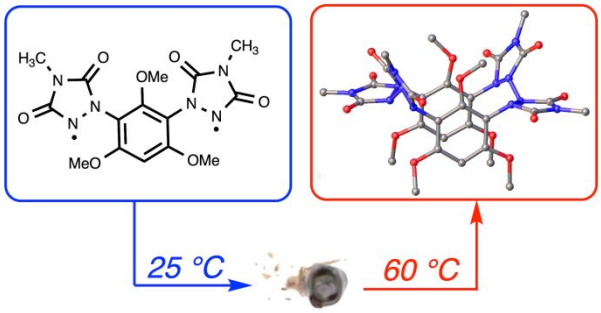


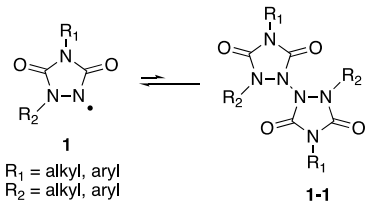
Abstract

Dynamic covalent chemistry (DCvC) describes systems in which readily reversible bond formation allows for control of product distributions by straightforward manipulation of reaction conditions (e.g., changes in temperature, solvent, concentration, etc.). Nitrogen-centered 1-aryl urazole radicals reversibly form tetrazane dimers in solution via N–N bond formation. When two such urazole units are attached to a single appropriately-substituted benzene ring the resulting diradical system engages in DCvC. At room temperature, a polymeric network of units is created that exhibits gel-like properties, while at higher temperatures near quantitative dimerization to

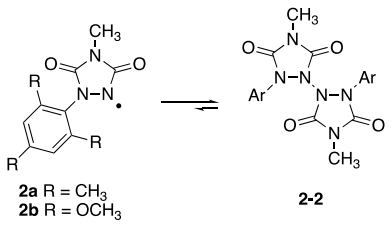
form a molecular cage is observed. However, attaching three such urazole units to a single appropriately-substituted benzene ring inhibits DCvC behavior.

Introduction

Urazole radicals (**1**) are persistent, highly colored, and air-stable nitrogen-centered radicals first reported by Pirkle in the late 1970's.[1] The radicals establish an equilibrium with the corresponding tetrazane N–N dimer, **1-1**, in solution. Appreciable concentrations of free radicals remain present in solution for urazole radicals **1** that are substituted with simple alkyl or aromatic substituents. Concentration of these solutions generally yields the corresponding colorless solid



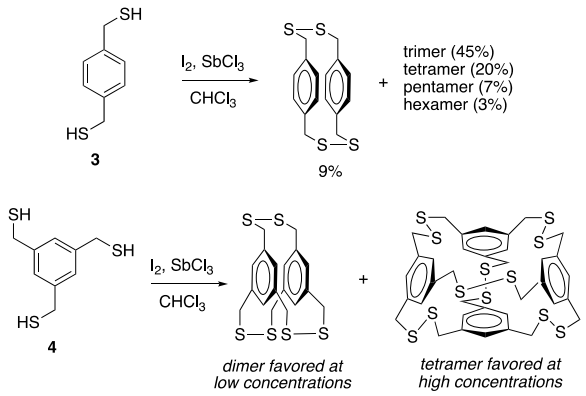
dimers **1-1**, while re-dissolution again establishes the equilibrium with the free radical. We have recently turned our attention towards the investigation of a subclass of these radicals, **2**, that bear aryl rings substituted at the 2, 4, and 6 positions relative to the attached urazole rings.[2,3] For these types of radicals, the solution equilibrium greatly favors the tetrazane dimer **2-2**. It has



been previously demonstrated that 1-*N*-aryl substituted radicals **1** (R_2 = aryl) are stabilized by delocalization of their spin character into the pi system of the benzene ring.[3] However, the ortho substituents on **2** prevent such stabilization due to the inability of the urazole ring to attain the required coplanarity with the benzene ring, and thus N–N bond formation is preferred. Interestingly, however, the N–N bond remains labile in solution so that combining separately prepared solutions of **2a** and **2b** leads to rapid equilibration with formation of a mixture of **2a**-**2a**, **2b**-**2b** and "crossed" dimer **2a**-**2b**.[3]

The ready reversibility of N–N bond formation in **2**-**2** suggested the possibility of urazole radicals joining a collection of other systems that exhibit behavior known as dynamic covalent chemistry (DCvC).[4,5,6,7] DCvC is a chemical phenomenon gaining much recent interest in which reversible covalent bond formation allows for the selective accessing of diverse molecular assemblies or product mixtures that are separately attainable by simple manipulation of reaction conditions (e.g., changes in temperature, solvent, concentration, etc.).[4,5,6,7] This approach has been used, among

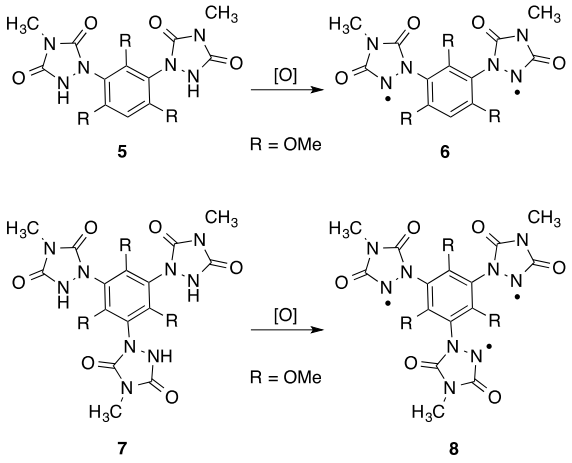
other things, to access structurally-interesting organic cages and cyclophanes. For example, Johnson has reported the formation of novel cyclic and caged disulfides upon oxidation of di- and tri-thiols such as **3** and **4** to the corresponding radicals (Scheme 1).[8,9] Pertinent to behavior characteristic of DCvC, the preference for dimer versus tetramer formation from **4** could be controlled by simple manipulation of the reaction mixture's concentration.



Scheme 1. Johnston's reported oxidations of di and tri-thiols, **3** and **4**, to form cyclic and caged products.

Johnston's finding stimulated our interest in investigating the fate of systems similar to **2** but containing more than one urazole radical site. While radicals have been investigated with regards to applications in DCvC, very few examples of nitrogen-centered radicals have been studied.[10,11] Furthermore, the lack of sensitivity of urazole radicals to oxygen (unlike most heteroatom radicals studied previously for DCvC

applications) could make them especially attractive as DCvC building blocks. To this end, we have synthesized and investigated the behavior of di- and tri-urazole radicals **6** and **8**, obtainable through oxidation of the corresponding urazoles **5** and **7** (Scheme 2), respectively, and herein report what we believe to be interesting and promising results.

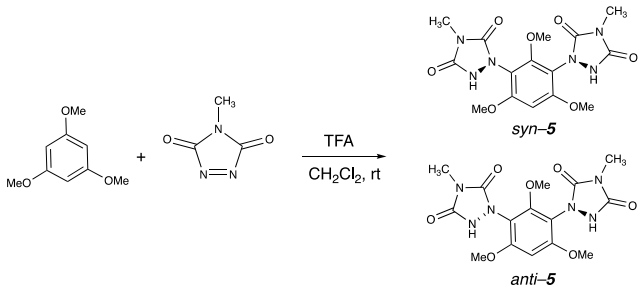


Scheme 2. Oxidation of diurazole **5** to afford diradical **6**, and triurazole **7** to afford triradical **8**.

Results and Discussion

*i. Synthesis and Reactivity of Diurazole Radical **6***

The stepwise reaction of two equivalents of MeTAD with 1,3,5-trimethoxybenzene in the presence of CF_3CO_2H afforded diurazole **5** in 83% overall yield (Scheme 3). Despite the



Scheme 3. Synthesis of *syn*- and *anti*-diurazoles **5**.

nominal symmetry of the diurazole's structure, the ^{1}H and ^{13}C NMR data clearly indicated that **5** exists as two slowly-interconverting, but physically inseparable, conformers that we assign as *syn* and *anti* based on the relative orientation of the two urazole ring systems. The *syn* form is C_s symmetric while the *anti* form is C_2 symmetric, and hence each exhibits a distinct N-Me and NH signal but the aryl H signals for both stereoisomers are isochronous. The four combined OMe groups of *syn*- and *anti*-**5** that are not sandwiched between the urazole rings reveal themselves as a broadened singlet at 3.85 ppm, while each of the two sandwiched OMe groups appear as sharp singlets at 3.81 and 3.79 ppm, respectively. The two conformers are found in a nearly equivalent 1.13:1 ratio as determined by integration. Likewise, the ^{13}C NMR spectrum revealed 18 carbon signals as closely spaced pairings of each of the expected 9 signals per conformer. Heating a DMSO-d_6 solution to 90°C was sufficient to collapse the two N-Me and NH signals to singlets but did not completely equilibrate the OMe signals indicating a significant barrier to rotation about the aryl–N bond likely due to the requirement for coplanarity of the urazole and benzene rings in a sterically crowded environment.

Diurazole **5** exhibits low solubility in CH_2Cl_2, the solvent we have typically employed for the oxidation of the NH urazole precursors of **1** and **2** with the heterogeneous oxidant nickel peroxide.[2] We surmised, however, that solubility of the initially formed monoradical (and then

diradical **6**) would be greater than that of **5**, and that any unreacted **5** could be removed at the end of the reaction during the filtration process required for removal of excess oxidant and its byproducts. Indeed, stirring a mixture of **5**, 4 equivalents of Ni_2O_3, and Na_2SO_4 (as drying agent) in CH_2Cl_2 resulted in consumption of **5** via TLC within 2 hrs. The solids were removed via filtration through a fine glass frit and the resulting colorless solution concentrated to a very thick viscous liquid. The ^1H NMR spectrum of the crude product exhibited a broad signal for the aryl H, broad multipeaked signals for the OCH_3 groups, and at least two inequivalent sized singlets for the N-Me groups (the NMR spectrum is provided in the Supporting Information). Assuming that molecules of **6** assume the same disposition towards N–N bond formation as was observed for **2**, this initially-formed product likely represents a mixture of randomly oligomerized molecular units. It was noticed upon removal of the NMR tube from the spectrometer that the initially fluid $CDCl_3$ solution of the product had become exceptionally viscous. Over the course of a night's standing the sample had become opaque in the NMR tube, and could be inverted without any apparent "run" of the gelatinous sample or escape of solvent down the sides of the tube. This experiment was repeated except upon concentration of the oxidized sample it was taken up in 0.5 mL CH_2Cl_2 (0.3 M) and the resulting clear colorless solution sealed in a vial (Figure 1A). Over 3 days the solution became thick and finally gelled

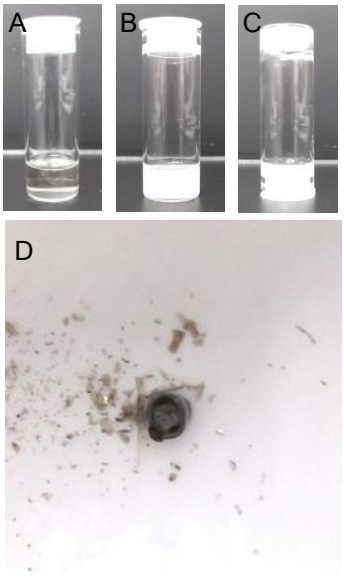


Figure 1. A) A clear, non-viscous solution of oxidized **5** just after sealing in a vial. B) After standing at rt for 3 days, now opaque and gelled. C) After being inverted for 24 hr with no obvious run of the material (cap at the bottom). D) The same sample after allowing the CH_2Cl_2 to evaporate, now a hard, dark–colored polymeric material.

into an opaque layer (Figure 1B) that could be inverted for up to 24 h without any apparent effect (Figure 1C) except an estimated 100 μL of solvent escaped from the suspended layer to the cap of the overturned sample. The gelling behavior is likely the result of diradicals **6**, via reversible N–N bond formation, transitioning from an initially unstructured assortment of oligomers to a more structured polymeric form that effectively traps solvent within. Indeed, when the cap securing the gelled sample was removed and the CH_2Cl_2 allowed to evaporate the sample collapsed into a hard, dark plastic-like polymer (Figure 1D). When this polymer was ground with a mortar and pestle, taken up in $CHCl_3$, and heated to reflux for 24 hours, a free-flowing white solid was obtained that proved to be a single compound. The same product was formed when a sample of the concentrated viscous liquid formed upon freshly oxidizing diurazole **5** was similarly heated in $CHCl_3$. The ^1H NMR spectrum for this new compound displayed a single sharp aryl H at 5.9 ppm, three separate sharp OMe signals at 3.89, 3.79, and 3.77 ppm (1:1:1

ratio), and two distinct *N*-Me signals at 3.24 and 3.22 ppm in a 1:1 ratio. The ^{13}C NMR spectrum similarly displayed two *N*-Me and three OMe carbon signals, along with four distinct carbonyl carbons and six inequivalent benzene ring carbons. When a saturated solution of this compound in CH_2Cl_2 was carefully layered with an equivalent volume of CH_3OH (in which it was insoluble) and the mixture allowed to stand at room temperature, clear plate-like crystals formed. Unfortunately, attempted isolation of these crystals resulted in their spontaneous and rapid degradation to a powdery white solid, apparently due to loss of volatile solvent molecules embedded within the crystal lattice. However, when a suitable crystal was selected and mounted quickly under a stream of cold nitrogen gas, it proved to be sufficiently stable for X-ray data collection. The crystal structure confirmed the compound to be dimer **6-6** resulting from joining the urazole units on opposing systems via two N–N sigma bonds such that the aromatic rings are superimposed (Figure 2). Two slightly different conformations of this face-to-face dimer were observed to be present within the unit cell, both nominally C_2 symmetric. One conformation positions the two benzene rings such that they are nearly perfectly eclipsed, while the other positions the two rings such that they are slightly rotationally staggered relative to one another. The planes defining the two benzene rings in the eclipsed conformer form a shallow angle of 14.4° (the distance widening from $d_{1\text{-}1'}$ to $d_{4\text{-}4'}$ in Figure 2A) while they are nearly parallel in the staggered conformation (2.7°). In both cases, the two urazole rings that form a chain of four nitrogen atoms connecting the two aromatic rings (*a*, *b*, *a'*, *b'* in Figure 2A) are oriented such that the nitrogen lone pairs within a common urazole ring (i.e., *a*, *b* and *a'*,*b'*) are anti to one another while the lone pairs between connected urazole rings (i.e. *b*, *b'*) are separated by approximately 120°.

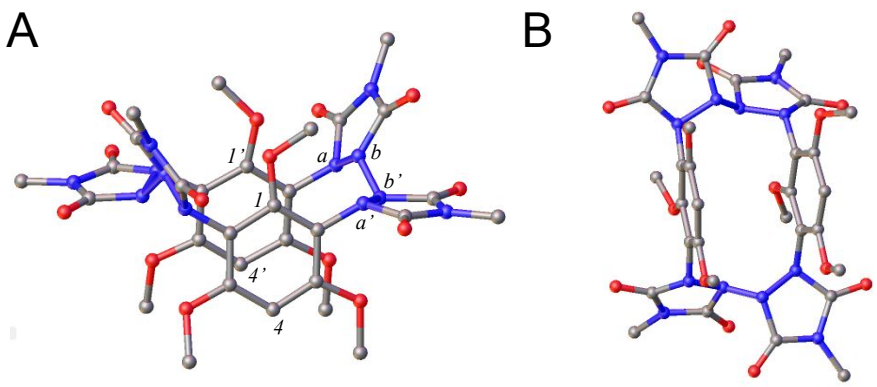


Figure 2. Structure of the eclipsed conformer of dimer **6–6** as generated from X-ray data from the front (A) and side (B) vantage points. Hydrogens are not shown for clarity. An ORTEP representation may be found in the Supporting Information. Images generated with Olex2 software.[12]

We found it intriguing that the preferred conformation for **6-6** was such that the two aromatic rings are superimposed face-to-face (as in Figure 3 where U = urazole ring) since an

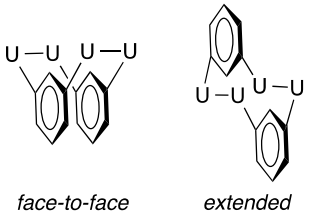


Figure 3. Two possible conformational isomers for dimer **6-6**

extended conformation appears to be a reasonable alternative that avoids unnecessary steric congestion. Using the X-ray crystal structures as starting input geometries, we modeled both of the face-to-face compounds at the M062X/6-31G(d) level of DFT theory. Both the eclipsed and staggered structures optimized to the same C_2 symmetric geometry with slightly staggered benzene rings. We also modeled the unobserved extended compound with C_{2h} symmetry. We confirmed that the face-to-face conformation is indeed 22 kcal/mol more stable than the extended stereoisomer. Generally, "sandwich-type" π-π stacking of aromatic rings as observed

in the face-to-face structure is disfavored relative to a parallel-displaced orientation, although some stabilization, particularly for substituted benzene systems, is still possible.[13,14] The center-to-center distance between the centers of the two benzene rings of the computationally–optimized (*in vacuo*) face-to-face isomer of 3.52 Å is slightly closer than the 3.6–3.8 Å range typically adopted by untethered substituted benzene dimers engaging in π-π stacking stabilization,[14] although the same distances in the experimental crystal structure geometries for the eclipsed (3.83 Å) and staggered (3.64 Å) conformers are consistent with the expected range of distances. Notably, the geometry of the extended structure forces a methoxy group from one of the aromatic rings to be suspended directly above the center of the other, thereby directing the oxygen lone pairs into the electron-rich π systems of the benzene rings (Figure 4). It is likely that the resulting electron-electron repulsion is responsible for raising the energy of the extended stereoisomer relative to the face-to-face isomer. The repulsive effect is also reflected in the length of the N–N bonds joining the two urazole units (i.e. *b,b'* as defined in Figure 2) as those in the extended conformation are lengthened (1.388 Å) relative to the corresponding bonds in the face-to-face conformation (1.369 Å).

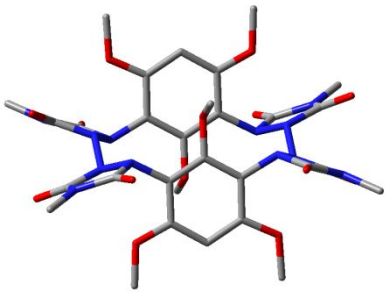


Figure 4. Optimized geometry of the unobserved extended conformation of dimer **6-6** depicting the repulsive oxygen lone pair/ benzene pi system interaction. Hydrogens are hidden for clarity.

Formation of **6-6** from the initially formed oligomeric product mixture requires ready reversibility of N–N bond formation. Thiophenol can act as a hydrogen atom donor to radical

sites and we investigated its use as a probe to determine the effective concentration of *N*–radical sites. As mentioned earlier, mixtures of dimers **2a**–**2a** and **2b**–**2b** rapidly scrambled to form crossed dimer **2a**–**2b** which suggested the presence of significant concentrations of unassociated radicals **2a** and **2b**. Indeed, addition of thiophenol to a solution of **2b** at room temperature resulted in rapid and quantitative conversion to the corresponding N-H urazole, along with $(PhS)_2$. Similarly, when a freshly oxidized (not heated) solution of diurazole **5** was treated with thiophenol at room temperature, we recovered **5** in 62% yield along with a 92% yield of byproduct $(PhS)_2$. However, thiophenol failed to reduce **6**-**6** even when the reaction mixture was heated in solution for 24 hr at 60°C. These results suggest that while freshly oxidized solutions of urazole **5** have *N*–centered radical sites readily available for reduction (and for reversible bond formation), once those sites have joined within the bonds between urazole units of **6**-**6**, any radical sites, if present at all via bond scission, must have an exceptionally low effective concentration.

*ii. Synthesis and Reactivity of Triurazole Radical **8***

When an additional equivalent of MeTAD was added to diurazole **5** at rt employing CF_3CO_2H as solvent, triurazole **7** was isolated in 91% yield as a white solid after 48 hrs of reaction time. The ^1H and ^{13}C NMR spectra again indicated a mixture of the two possible conformers, in an approximate 3:1 ratio with the all-*syn* isomer being the minor component. Oxidation of **7** (as indicated by loss of N-H signals in the ^1H NMR spectrum) with Ni_2O_3 was both slow and ineffective at room temperature likely due to the low solubility of **7**. Therefore, we instead refluxed a mixture of **7** and Ni_2O_3 in $CDCl_3$ (as solvent) and followed the progress of

the reaction by ^{1}H NMR spectroscopy. After 24 hrs of heating, ^{1}H NMR spectral analysis revealed two very complex clusters of signals centered at approximately 4 ppm (for the OMe groups) and 3.1 ppm (for the *N*-Me groups). Continued heating of the mixture led to a decrease in complexity of signals in the ^{1}H NMR spectrum and gradual emergence, and ultimately predominance, of two sharp singlets, at 3.96 (OMe) and 3.24 (*N*-Me) ppm over a period of three days. Column chromatography of the crude reaction mixture afforded a white solid in low yield (27%), with the remainder being uncharacterized polymeric material. As with dimer **6-6**, while this compound afforded needle-like crystals upon slow evaporation from solution, the crystals rapidly degraded upon attempted isolation. Again, however, rapid cooling of the crystal in the X-ray diffractometer allowed for data collection and confirmation of its structure as suspected cage-like dimer **8-8** (Figure 5). Unlike **6-6**, however, a single conformer of the structure was observed in which the two benzene rings are nearly perfectly eclipsed. The center-to-center distance between the two rings of 3.636 Å was slightly shorter than that of **6-6**, with the planes defining the two benzene rings being nearly parallel (2.2°). Interestingly, the average bond length of the N–N bonds connecting the three sets of urazole units of 1.374 Å was even shorter than those of **6-6** (1.385 Å).

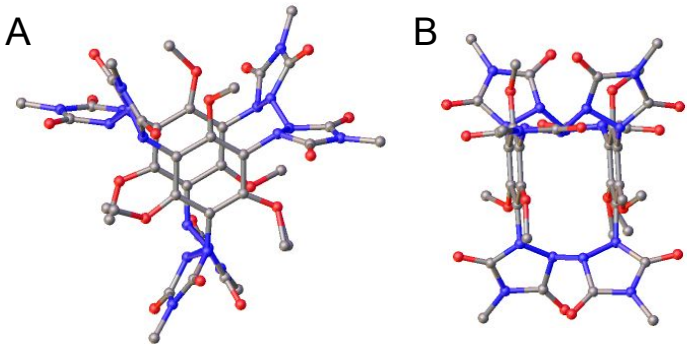


Figure 5. Structure of dimer **8**–**8** as generated from X-ray data from the front (A) and side (B) vantage points. Hydrogens are not shown for clarity. An ORTEP representation may be found in the Supporting Information. Images generated with Olex2 software.[12]

When triurazole **7** was heated to reflux in $CHCl_3$ with Ni_2O_3 for 24 hr, filtered, and concentrated, a quantitative yield of a polymeric product was obtained. When this crude product was taken up in 0.5 mL of CH_2Cl_2 and then sealed in a vial (as was done upon oxidation of diurazole **5**), no gelling of the solution was observed. Additionally, if a similar mixture was heated for 24 hr, the Ni_2O_3 removed via filtration, and the resulting filtrate heated for an additional 2 days (akin to what worked for a high yield synthesis of **6-6**) only a poor yield (< 6%) of **8-8** was obtained. Since a greater yield (27%) of **8-8** was obtained upon continued heating in the presence of Ni_2O_3 (as described above), this would suggest that incomplete oxidation of **7** plagues these reactions, because otherwise the yields would be equivalent. Given these results, and unlike what was observed for **6-6**, therefore, it remains unclear as to whether oligomers formed from oxidized **7** are capable of ultimately generating dimer **8-8** via DCvC.

Finally, we should note that the structure of **8-8** is similar to that of the dimer formed from the trithiol **4** (Scheme 1).[9] The center-to-center distance in that hexasulfide was found to be 3.73 Å and the benzene ring planes at a 2° angle relative to one another.

Conclusions

Urazole radicals have been shown to exhibit reactivity consistent with dynamic covalent chemical behavior. This was first observed when it was demonstrated that mixtures of solutions of **2a-2a** and **2b-2b** resulted in the formation of "crossed" dimer **2a-2b**. Attaching two urazole radical units onto the same aromatic ring as in **6** allows for exhibition of gelling behavior at room temperature, while at higher temperatures the equilibrium is shifted towards formation of dimer **6-6**. The gelling behavior at room temperature is best explained by assuming N–N bond

formation between the N–centered radical sites of nearby molecules of **6** to form a polymeric network that effectively traps solvent molecules. Because of the ready reversibility of N–N bond formation, heating solutions of this compound allows for individual molecules of **6** to sample intermolecular bond formation and ultimately shift the equilibrium towards formation of dimer **6-6**. However, three urazole units attached onto the same aromatic ring as in **8** appears to dampen the ability of this system to engage in the fluid reactivity required for DCvC behavior.

Experimental Section

General Methods. Column chromatography was conducted on silica gel (234-400 mesh). Thin-layer chromatography was performed on precoated silica gel plates (250 mm) and visualized by ultraviolet light. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer. Chemical shifts are reported in units of parts per million downfield from TMS. High-resolution mass spectra (HRMS) were acquired via electron spray ionization on an LTQ-FTMS hybrid mass spectrometer. *N*-Methyl-1,3,5-triazoline-3,5-dione (**2**) was synthesized via oxidation of *N*-methylurazole with DABCO-Br_2 as described in the literature.[15,16] All other chemicals and solvents were obtained from commercial sources and used without further purification unless otherwise noted.

Synthesis of 4-methyl-1-[2,4,6-trimethoxy-3-(4-methyl-3,5-dioxo-1,2,4-triazolidin-1-yl) phenyl]-1,2,4-triazolidine-3,5-dione (5). To a stirring

solution of 0.235 g (1.4 mmol) of 1,3,5-trimethoxybenzene and 0.16 g (1.4 mmol) of MeTAD in 15 mL of 1,2-dichloroethane was added 0.22 mL (2 equiv) of CF_3CO_2H via syringe. The initial red color of the solution dissipated within 1 min to afford a clear colorless solution. A second equivalent (0.16 g) of MeTAD was added and the solution stirred for 4 hours until a faint pale pink color persisted. Concentration of the reaction mixture afforded an off white solid that was taken up in 40 mL of EtOAc and the mixture boiled briefly. After cooling, filtration, and washing with additional EtOAc, **5** was afforded as 0.46 g (83% yield) of a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ [a 1.13:1 mixture of two slowly interconverting conformational isomers] 10.82 (s, 1H), 10.77 (s, 1H), 3.79–3.85 (three singlets. 9H), 2.98 (s, 3H), 2.97 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [a 1.13:1 mixture of two slowly interconverting conformational isomers]159.8, 159.7, 158.3, 154.1, 154.0, 153.8, 153.8, 110.3, 110.1, 92.4, 92.4, 62.3, 62.11, 56.8, 56.7, 24.9, 24.9; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{19}N_6O_7$ 395.1310; Found 395.1303.

Synthesis of 4-methyl-1-[2,4,6-trimethoxy-3,5-bis(4-methyl-3,5-dioxo-1,2,4-triazolidin-1-yl)phenyl]-1,2,4-triazolidine-3,5-dione (7). To a stirring solution of 0.200 g (5.08 mmol) of diurazole **5** in 2 mL of

trifluoroacetic acid was added 75 mg (1.3 equiv) of MeTAD. The red solution was stirred at room temperature for 2 days. The resulting pale pink solution was concentrated with a stream of dry N_2 to a pink glass. CH_3OH (10 mL) was added, the contents swirled, and the solution concentrated on a rotary evaporator. This process was repeated two additional times. To the resulting foamy white product was added 10 mL of EtOAc. The sides of the flask were scraped to free clung material and the mixture swirled until a white free flowing precipitate developed. Filtration afforded 0.134 g of a white solid. The filtrate was allowed to stand for approximately 1 hr as additional precipitate formed. Filtration afforded 85 mg of additional product, and a third crop afforded another 32 mg of product. Combining these samples afforded 0.251 g (91% yield) of **7** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ [a 3:1 mixture of two slowly interconverting conformational isomers] 10.86–10.97 (3 singlets, 3H), 3.84–3.86 (2 singlets, 9H), 2.99–3.01 (3 singlets, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ [a 3:1 mixture of two slowly interconverting conformational isomers] 159.5, 159.4, 155.4, 155.1, 154.7, 154.4, 154.3, 154.0, 117.5, 117.5, 117.2, 62.6, 62.3, 62.3, 25.1, 25.1. HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{18}H_{21}N_9O_9Na$ 530.1354; Found 530.1354.

Oxidation of Diurazole 5. To a stirring mixture of 50 mg (0.15 mmol) of **5** and 0.2 g Na_2SO_4 in 10 mL of CH_2Cl_2 was added 180 mg (4 eq) of Ni_2O_3 (~30% active oxidant). The mixture was stirred vigorously for 2 hrs and then filtered through a fine glass frit under N_2 pressure. The reaction mixture and filtered solids were washed with an additional 15-20 mL of fresh CH_2Cl_2 and similarly filtered to provide a clear, colorless solution. Separate batches were treated differently as discussed in the text:

(a) Concentration of the solution afforded a very thick viscous liquid. ^{1}H NMR ($CDCl_3$) δ 6.41 (v br s, 1H), 3.6–4.0 (broad multipeaked signal, 9H), 3.0–3.2 (broad multipeaked signal, 6H). The sample solution became very viscous within 15-20 minutes.

(b) The solution was concentrated to 0.5 mL, transferred to a vial, and sealed with a cap. The solution became very viscous and slowly turned opaque. On the 3rd day, the completely opaque white sample could be inverted with no run of the sample down the sides of the vial over a 24 hr period, although some CH_2Cl_2 (~ 100 μL) escaped. Removal of the cap and spontaneous evaporation of the CH_2Cl_2 resulted in formation of a hard, dark-colored, plastic-like ball (40 mg). This plastic material was crushed with a mortar and pestle, taken up in 15 mL of $CHCl_3$, and the mixture heated for 24 hr. Upon cooling and concentration, 38.7 mg of a white free-flowing solid was isolated that was identical to dimer **6-6** described below.

(c) When a similarly formed sample was generated from 25 mg of **5** and 90 mg of Ni_2O_3, taken up in 5 mL of CH_2Cl_2, briefly deoxygenated with a stream of dry N_2, and treated with 20 μL (3 eq) of thiophenol, the solution turned cloudy within an hour. After stirring for 24 hr, the sample was concentrated using a stream of dry N_2 gas to afford a white solid. 10 mL of CH_2Cl_2 and 10 mL of a 0.1 M aq. NaOH solution were added to the sample. The organic layer was separated, and the aqueous layer washed 1 × 5 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 12.7 mg (92% yield) of diphenyl disulfide as a white solid. TLC and ^{1}H NMR spectrum were identical to an authentic sample. The aqueous layer was acidified with conc HCl and washed 10 × 10 mL CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to afford 15.4 mg (62% recovery) of **5** as a white solid.

Dimer 6-6. To a stirring mixture of 86 mg (0.25 mmol) of **5** and 0.5 g Na_2SO_4 in 20 mL of CH_2Cl_2 was added 310 mg (4 eq) of Ni_2O_3 (~30% active oxidant). The mixture was stirred vigorously for 2 hrs and then filtered through a fine glass frit under N_2 pressure. The reaction mixture and filtered solids were washed with an additional 15-20 mL of fresh CH_2Cl_2 and similarly filtered to provide a clear, colorless solution. The solution was concentrated to clear viscous liquid, taken up in 20 mL of $CHCl_3$ and heated (heating mantle) to reflux for 24 hours with a drying tube in place. The solution was cooled to room temperature and concentrated to afford 85 mg (99% yield) of **6-6** as a white, free-flowing solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 2H), 3.88

(s, 6H), 3.78 (s, 6H), 3.77 (s, 6H), 3.24 (s, 6H), 3.22 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5, 159.2, 159.8, 154.1, 154.0, 153.6, 153.0, 110.5, 109.0, 62.8, 57.4, 56.7, 26.3, 26.2. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{30}H_{33}N_{12}O_{14}$ 785.2237; Found 785.2226.

Attempted Reduction of Dimer 6-6. A solution of 9 mg (0.011 mmol) of **5** in 2 mL of $CHCl_3$ (freshly run through a column of dry Al_2O_3 to remove EtOH stabilizer) in a sealable screw-cap high-pressure tube was deoxygenated with a stream of dry N_2. To the solution was added 7 μL (6 eq) of thiophenol via syringe. The solution was again briefly deoxygenated. The tube was sealed and heated in a specially designed form-fitting steel cylinder at 60 °C for 24 hr. Upon cooling, no precipitate was observed to have formed. The reaction mixture was concentrated with a stream of dry N_2 and the residue examined by ^{1}H NMR spectroscopy. Only starting dimer **6-6** and traces of thiophenol were observed.

Dimer 8-8. To a stirring mixture of 50 mg (98.6 μmol) of **7** and 100 mg Na_2SO_4 in 15 mL of $CHCl_3$ (filtered through a column of Al_2O_3 to remove EtOH stabilizer) was added 180 mg (6 eq) of Ni_2O_3 (~30% active oxidant). The reaction flask was fitted with a condenser and drying tube and the contents heated (heating mantle) to reflux for 3 days. The reaction mixture was filtered through a short column of celite supported by a fine glass frit under N_2 pressure. The filtered solids were washed with an additional 10-15 mL of fresh CH_2Cl_2, and the combined washings concentrated

to a white solid. Column chromatography (SiO_2, EtOAc) afford 13 mg (27% yield) of **8-8** as a white crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 9H), 3.24 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3, 154.3, 153.3, 113.9, 63.7, 26.5. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{36}H_{37}N_{18}O_{18}$ 1009.2528; Found 1009.2523.

Computational details. All geometry minimizations were carried out using the Gaussian 16suite of software and conducted at the M06-2X/6-31G* level. Frequency calculations were carried out at the same level of theory to ensure that the geometry represented a true minimum (i.e., no negative frequencies).[17]

SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra for all newly characterized compounds. Cartesian coordinates, single-point energies for all computationally minimized structures.

This material is available free of charge via the Internet at http://pubs.acs.org.

CCDC 2006212 and 2006213 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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