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Communication

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Phenazine-1,6-dicarboxamides: redox-responsive molecular switches

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Supporting Information Placeholder

ABSTRACT: We introduce phenazine-1,6-dicarboxamides as redox-responsive molecular switches. Reduction of their phenazine core transforms it from a hydrogen bond acceptor into a hydrogen bond donor and thus forces the secondary amide substituents to turn around. The resulting conformational changes are envisioned to form the basis for butterfly-coil foldamers undergoing reversible extension and contraction in response to changing their oxidation state.

Foldamers[1] capable of changing their linear dimensions quickly and reversibly in response to an external stimulus may be viewed as molecular actuators,[2] which could form the basis for designing artificial muscles and other functional materials.[3] Existing stimuli-responsive foldamer designs incorporate molecular switches that change their conformation in response to irradiation,[4] protonation,[5] or introduction of other ions,[6] or neutral organic molecules.[7,8] However, from the practical standpoint, the most convenient way to stimulate a molecular actuator would be via a redox process, which could be achieved electrochemically and reversed simply by switching the direction of electric current. Furthermore, it would be desirable to design a system that would not require the migration of large ions, but rely only on the flow of electrons and protons. In this Communication, we describe a new type of molecular switch that satisfies these requirements.

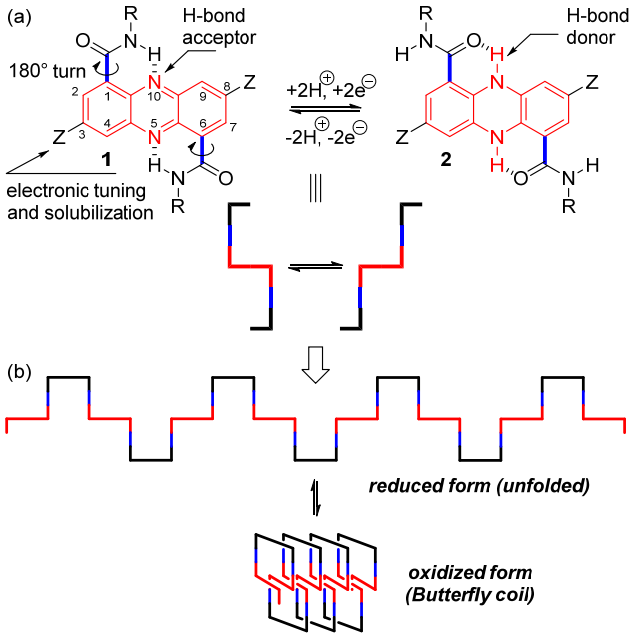
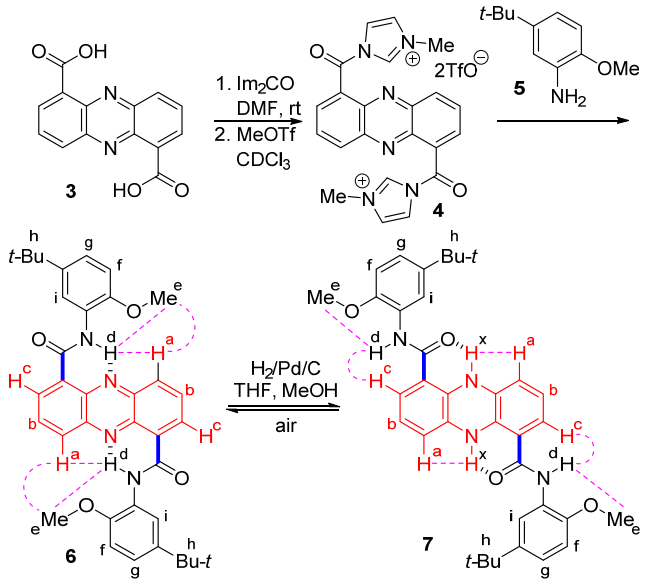


Figure 1. Phenazine-based molecular switch and butterfly-coil folding geometry.

Our basic design is illustrated in Figure 1a. The phenazine nitrogens in structure **1** serve as hydrogen bond acceptors and thus determine the orientation of the adjacent carboxamide moieties. The reduced 5,10-dihydrophenazine form (**2**), on the other hand, functions as a double hydrogen bond donor, which favors the opposite orientation of the amide groups.[9] Thus, reduction-oxidation of this system will be accompanied by ca. 180° rotation of the two parallel bonds shown in blue. A chain composed of such molecular switches and cisoid spacers (shown in black) is predicted to fold in a butterfly-coil fashion, i.e., forming loops with regularly alternating chirality (Figure 1b).[10]

To test the basic premise of our design, we first synthesized model bis-amide **6** via the route shown in Scheme 1. Hydrogen bonding between the amide protons and the adjacent phenazine nitrogens and methoxy groups was predicted to favor the desired doubly folded conformation. Indeed, the NOESY spectrum of **6** contained the diagnostic interactions shown in purple (**a**—**d**, **d**—**e**, **e**—**a**), which confirmed the expected geometry. Next, we set out to demonstrate the unfolding of model compound **6** under reducing conditions. To this end, we chose catalytic hydrogenation, so as to avoid by-products that would complicate the subsequent isolation and NMR analysis. Stirring **6** under 20 psi of hydrogen in the presence of palladium on carbon converted it cleanly to the highly air-sensitive dihydrophenazine **7**. To our satisfaction, the NOESY spectrum of **7** displayed interactions between the amide protons **d** and *ortho*-protons **c**, indicating that the expected unfolding did indeed take place. Upon exposure to air, **7** reverted cleanly to **6**.



Scheme 1. Proof-of-principle study

With these results in hand, we proceeded to design a symmetrical spacer that would encourage the phenazine moieties to stack in an

offset, antiparallel orientation, as required by the butterfly coil geometry represented schematically in Figure 1b. With the help of computer-assisted modeling, we identified xanthene-4,5-diamines as promising candidates for this role. For example, tetramer **8** (depicted in Figure 2 in extended form for ease of illustration) was predicted to fold as shown below.

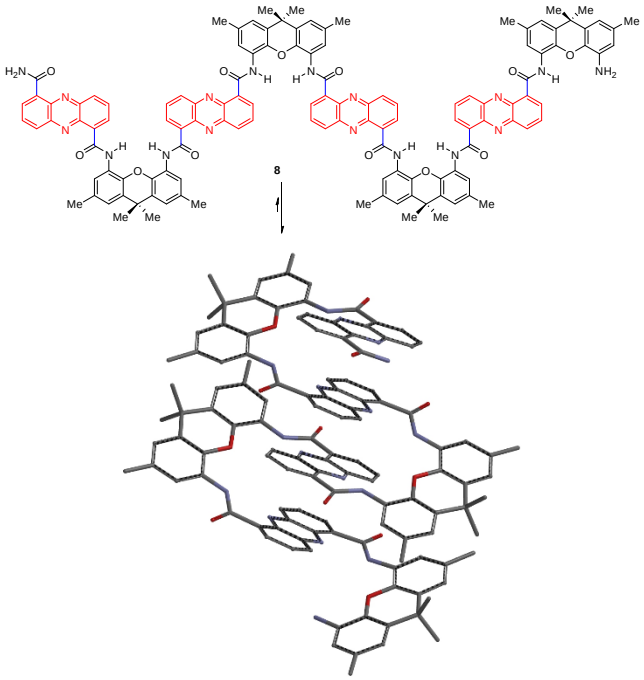
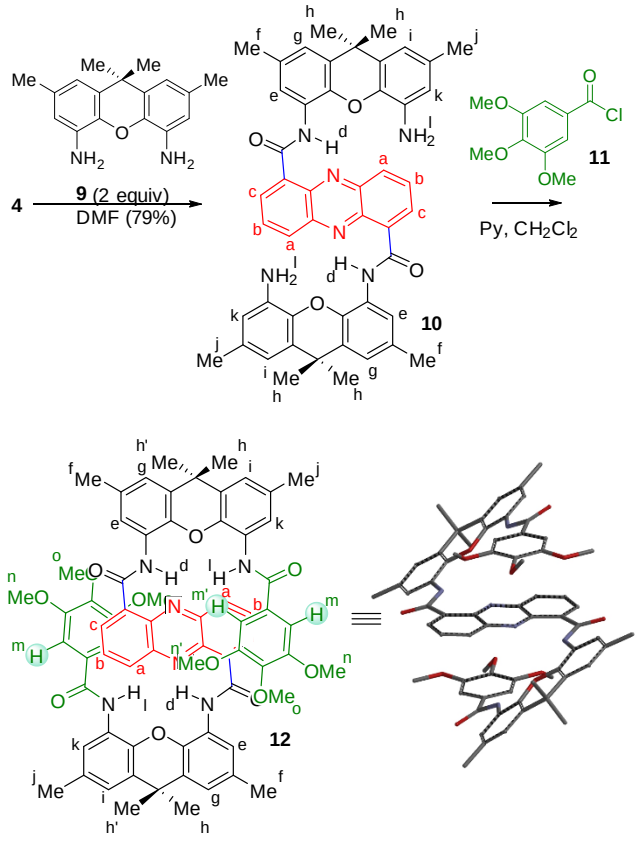


Figure 2. Predicted folded structure of tetramer **8**.



Scheme 2. Synthesis of single unit model **12.**

Coupling **4** with two equivalents of 2,7,9,9-tetramethylxanthene-4,5-diamine **9** afforded symmetrical derivative **10**. In contrast to **6**, which is essentially flat, the xanthene moieties in compound **10** are twisted significantly out of the plane of the phenazine nucleus (ca. 33° dihedral angles, according to DFT calculations). Geometry optimization predicted two stable conformers of **10**: a C_2-symmetrical one, with the two amino groups positioned over the same face of the phenazine, and a centrosymmetrical one, in which the amino groups are on the opposite faces. It is the latter conformation that corresponds to the geometry of each phenazine unit in the proposed butterfly coil. Computer-assisted modeling indicated that transforming the amines into benzamide moieties, which cannot fit on the same face of the phenazine nucleus, would effectively ensure that the product would adopt the desired centrosymmetrical conformation exclusively.[11] With this in mind, diamine **10** was subjected to bis-acylation with 3,4,5-trimethoxybenzoyl chloride **11** to afford **12** as a bright-red crystalline solid.

X-ray crystallography confirmed that compound **12** adopted the expected folded conformation in solid state (Figure 3). The trimethoxyphenyl groups were found in a parallel, slightly offset face-to-face orientation relative to the central pyrazine ring, with ca. 3.7 Å distance between the centers, consistent with π-stacking. The C1/C6 carboxamide groups formed hydrogen bonds to the phenazine nitrogens and the xanthene oxygens, estimated at ca. 1.9 Å and 2.3 Å, respectively, in complete agreement with computer modeling.

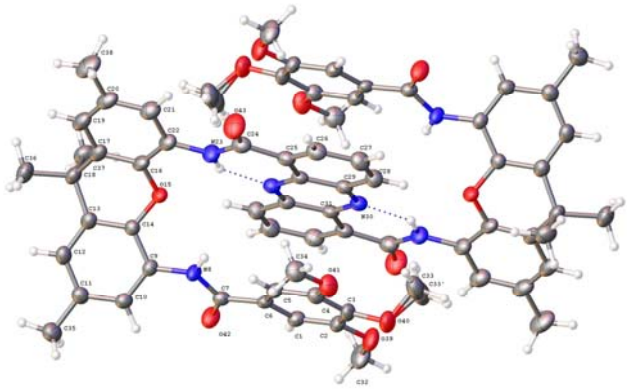


Figure 3. X-ray structure of **12.**

The folded conformation was found to be favored in solution as well. The ^{1}H NMR spectrum of **12** in $CDCl_3$ revealed that *ortho*-protons **m**/**m′** were strongly shifted upfield (δ 5.8 ppm vs. δ 7.3 ppm in simple 3,4,5-trimethoxybenzamides), presumably due to shielding by the phenazine nucleus. The shielding effect persisted in the presence of protic and polar solvents (80% CD_3OD-20% $CDCl_3$, DMSO-d_6). Moreover, the chemical shifts of **m**/**m′** were not affected appreciably by temperature changes when heated up to 75 °C in DMSO-d_6 or cooled down to –75 °C in CD_2Cl_2. A NOESY spectrum of **12** confirmed the proximity of both sets of amide protons (**d** and **l**) to each other and to the **a** protons on the phenazine nucleus.

It should be noted that the point symmetry of the folded structure of **12** is expected to render geminal methyl groups **h** and **h′** on the xanthene moieties diastereotopic. However, at ambient temperature they produce one sharp singlet in ^{1}H NMR, and only begin to separate into a diastereotopic pair at –42 °C (Figure 4), which translates into an energy barrier of 10.9 Kcal/mol, according to the Eyring-Polanyi equation.[12] This observation indicates that the folded conformation, although thermodynamically favored, is kinetically quite mobile. This allows the xanthene moieties to flip rapidly on NMR timescale resulting in the interconversion of two degenerate centrosymmetrical conformers **X** and **X′**, as illustrated

schematically in Figure 5. As an aside, it may also be observed that the signals due to aromatic protons **m**/**m′** and methyl groups **n**/**n′** broaden around –65 °C as the rotation of the trimethoxyphenyl groups slows down.

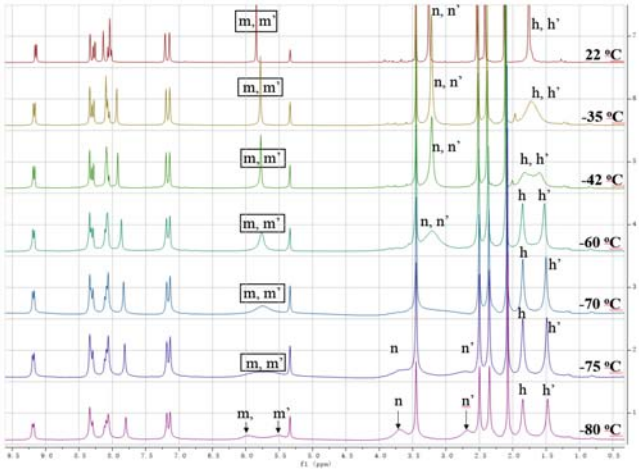


Figure 4. Variable-temperature experiment (300 MHz).

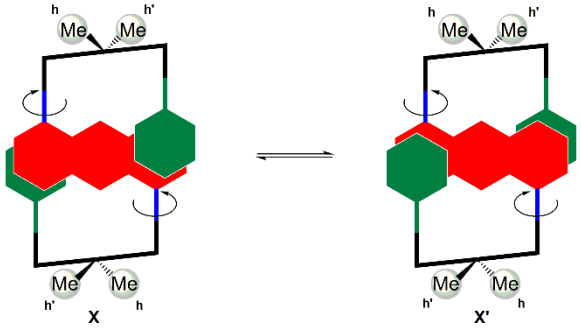
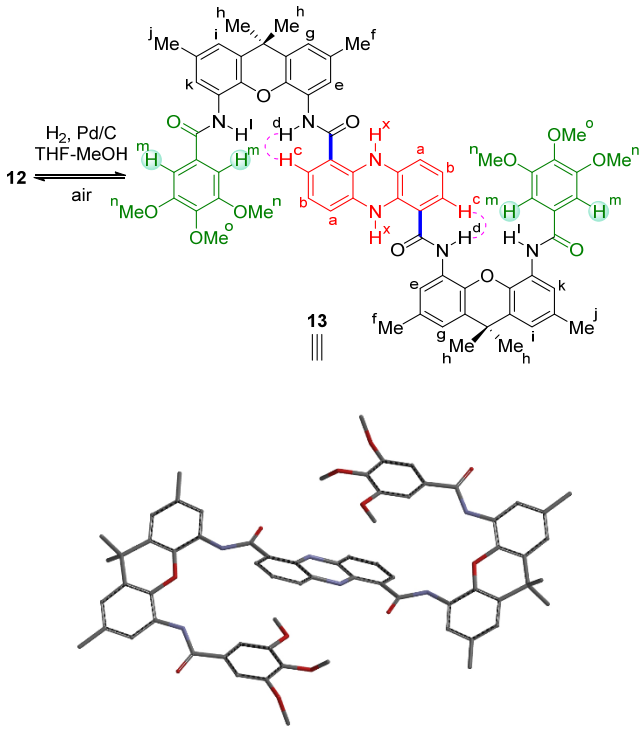


Figure 5. Double flip



Scheme 3. The unfolding of **12**.

Our next objective was to demonstrate the opening of the single unit model in response to reduction. Catalytic hydrogenation of **12** was carried out similarly to that of **6** to give rise to the expected dihydrophenazine **13** (Scheme 3). As the first sign of its conformational change, we observed that aromatic protons **m** shifted from 5.8 to 7.0 ppm, which was consistent with the expected structure with diminished shielding. Furthermore, the two sets of amide protons (H^d and H^l) no longer displayed NOE with protons **a**. Instead, NOESY indicated the proximity of amide protons **d** to aromatic proton **c** on the dihydrophenazine nucleus. As with the simpler model (cf. **7** above), dihydrophenazine **13** quickly oxidized back to **12** on exposure of its solution to air.

In conclusion, we have demonstrated the feasibility of using phenazine-1,6-dicarboxamides as redox-responsive molecular switches. Our current efforts are focused on optimizing the design of the cisoid linkers and the phenazine building blocks and assembling them into short oligomers. We are also exploring electrochemical methods for their reduction-oxidation.[13] Our studies in these directions will be published in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information (experimental procedures, computational studies, characterization data, NMR spectra, and X-ray crystallographic data for **12**) is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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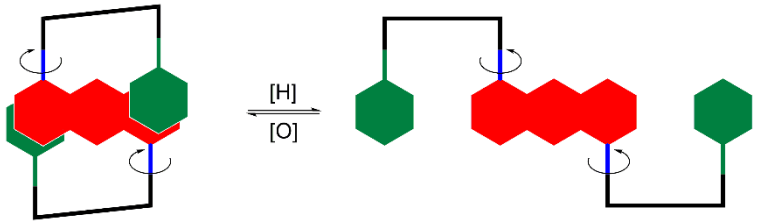
13. For cyclic voltammetry data of **1a** (R = *n*-butyl), see Supporting Information.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