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# *N*-Salicylideneanilines: Tautomers for Formation of Hydrogen-Bonded Capsules, Clefts, and Chains

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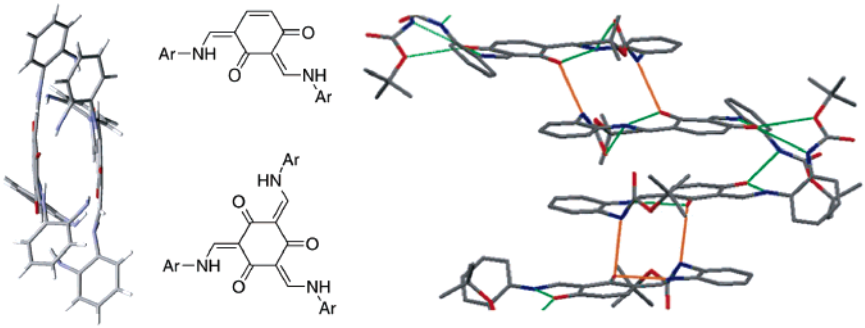


The synthesis, characterization, and solid-state structures of new salicylaldimines are reported. Bis(*N*-salicylideneaniline)s (BSANs) and tris(*N*-salicylideneaniline)s (TSANs) are sterically encumbered compounds featuring a central six-membered ring in the keto-enamine tautomer. When extended with additional functional groups, these molecules may form hydrogen-bonded capsules, clefts, and extended structures. A TSAN with *N*-$^t$BOC-*o*-phenylenediamine groups has been structurally investigated. The complementary hydrogen-bonding motif in this molecule leads it to form dimers in solution and in the solid state. A BSAN with *N*-$^t$BOC-*o*-phenylenediamine substituents forms a hydrogen-bonded cleft in solution but forms an extended hydrogen-bonded ladder assembly of cofacial dimers in the solid state. When *N*-$^t$BOC-1,8-naphthalenediamine was utilized to extend the cleft, an unusual perimidine structure was obtained with the central core in the enol tautomer. In addition, ab initio calculations have been used to support the assignment of the keto-enamine or enol-imine tautomers of the BSANs and TSANs and to predict tautomerization in related BSANs and TSANs.

## Introduction

Tautomers are readily interconverted constitutional isomers, usually distinguished by a rearrangement of a labile hydrogen atom and a double bond (e.g., keto-enol tautomerization).[1] The equilibrium between tautomers is often rapid under normal conditions, being catalyzed by traces of acid or base present in most samples and solvents.[2] Often one isomer is strongly favored (acetone, for example, is 99.999% keto tautomer). Proton tautomerization is one of the most thoroughly studied equilibrium processes because of its crucial importance to several fields of chemistry and biochemistry; it is implicated in pharmaceutical effects, enzyme activity, stabilization of DNA, and self-assembly.[3−5]

Over the past decade a great effort has been devoted to explore the central role hydrogen-bonding plays in the self-

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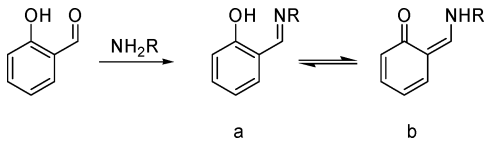
assembly of molecules into supramolecular aggregates. Several elegant routes toward hydrogen-bonded solution aggregates, engineered crystals, liquid crystals, and two- and three-dimensional extended solids have been reported.[6−9] The major key in this respect is the design of modules that are capable of forming multiple hydrogen bonds and allow control over the assembly of the desired secondary structure.

Molecular containers are of particular interest because of their potential application in various areas ranging from drug delivery and catalysis to molecular recognition and host−guest interactions.[10] Functionalized calixarenes represent a well-established motif for the formation of hydrogen-bonded molecular containers, and their properties and applications have been described in a large number of publications.[11]

*N*-Salicylideneanilines represent another interesting class of compounds possessing intramolecular hydrogen-bonding. These molecules are prepared by the condensation of salicylaldehyde with primary amines, as shown in Scheme 1. The interest in these substances arises from the fact that they can undergo reversible proton transfer (tautomerism) leading to interesting properties such as thermo- and photochromism, making these molecules potential candidates for optical switches and storage devices.[12−14] They show equilibrium between the enol-imine (OH) form and the keto-enamine (NH) form, with the enol-imine form generally being the most stable form at room temperature (Scheme 1).[15] As a result, the OH form of *N*-salicylideneanilines has been well-characterized, but until recently, no purely NH form had been structurally characterized.[16] In fact, the confirmation of a *N*-salicylideneaniline exclusively in the NH form in the solid state has been controversial.[17−19]

**SCHEME 1. Condensation of a Salicylaldehyde with a Primary Amine**




The assembly of sterically crowded aromatics is an attractive route to discotic columnar materials, foldamers, and donor-$\sigma$-

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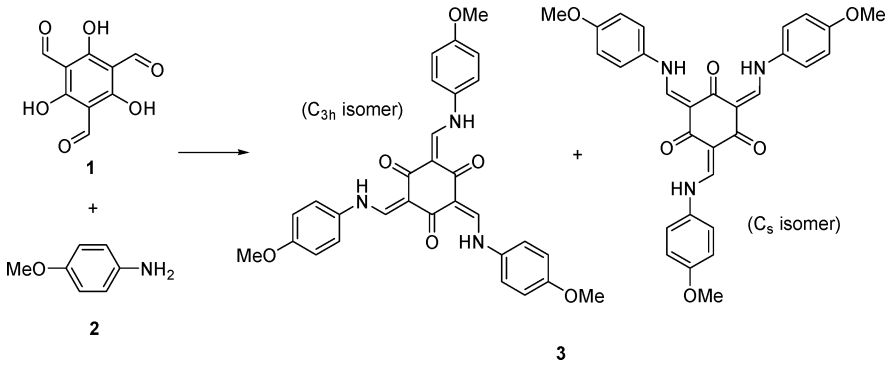
**SCHEME 2. Synthesis of Keto-Enamine Tris(*N*-salicylideneaniline)s**




acceptor chromophores. In most cases hexasubstituted aromatics, such as 1,3,5-benzenetriamides or 1,3,5-benzenetriols, are used as suitable cores, which upon further functionalization self-assemble into well-defined secondary conformations.[20]

We recently communicated a convenient synthesis of triformylphloroglucinol **1**. Upon reaction with aniline derivatives, this sterically encumbered molecule does not form tris(imine)s but rather affords tris(*N*-salicylideneaniline)s (TSANs) (e.g., **3**) that are exclusively found in the keto-enamine (NH) form. They are formed as a mixture of two geometrical isomers with approximate $C_s$ and $C_{3h}$ symmetry (Scheme 2). In the $C_{3h}$ isomer, all of the carbonyl groups on the central ring are involved in intramolecular hydrogen-bonding.[16] Yelamaggad et al. recently demonstrated that when the aromatic substituents are highly branched, TSANs form discotic liquid crystalline phases.[21] These molecules possess multiple hydrogen-bonding groups around a rigid central core, suggesting their use in developing hydrogen-bonded capsules and assemblies.

Here, we report our studies on TSANs and bis(*N*-salicylideneaniline)s, BSANs, as well as their assembly into hydrogen-bonded structures. Their complementary hydrogen-bonding motifs lead them to form capsule-like dimers and clefts in solution. We have performed the first calculations of tautomers of TSANs and BSANs to determine their relative stabilities and to compare their calculated geometries with those determined from single-crystal X-ray diffraction (SCXRD). These molecules are new, modular motifs for the formation of supramolecular structures.

## Results and Discussion

**TSANs.** To initiate this work, 1,3,5-triformylphloroglucinol **1** was required. Although this molecule was previously prepared in seven steps from 1,3,5-trichlorobenzene,[22] with an overall yield of 21%, the product was not characterized. We discovered that compound **1** could be readily prepared in nearly pure form in a single step from phloroglucinol under Duff formylation[23] conditions.[16]

The reaction of **1** with **2** in refluxing ethanol afforded the TSAN **3** in 52% yield. The IR spectrum of this yellow-orange, fluorescent compound confirmed the disappearance of an aldehyde, an intense absorption band observed at 1641 $cm^{-1}$ in **1**. As we initially expected the enol-imine form for **3** to be the only product formed, the $^1H$ NMR spectrum of **3** (Figure 1)

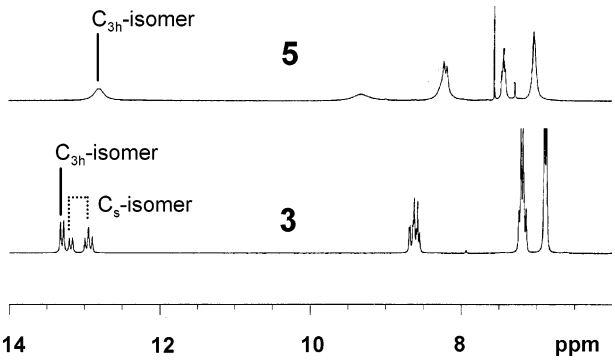



**FIGURE 1.** $^1H$ NMR spectra of compounds **3** and **5** ($CDCl_3$, 300 MHz).

was surprisingly complicated. The enol-imine form for **3** would be expected to show singlets for the imine and phenol in the OH form, but instead the spectrum showed multiple peaks between $\delta$ 8.5−9.0 and $\delta$ 12.8−13.5 ppm. 2-D NMR experiments showed that only the keto-enamine (NH) form of **3** is present, in a mixture of two geometrical isomers with $C_{3h}$ and $C_s$ symmetries, as shown in Scheme 2. The carbonyl group of the central ring was observed in the $^{13}C$ NMR spectrum at ∼185 ppm, characteristic of a carbonyl group rather than a phenol (this resonance is observed at 174 ppm in **1**). Interestingly, *J*-coupling ($^3J_{HH}$ ∼13.5 Hz) was observed between the vinylic protons and the NH protons of **3**. This strong coupling is consistent with localization of the proton on the nitrogen atom and slow exchange. Indeed, the 100% keto-enamine form for an *N*-salicylaldimine is expected to show a $^3J_{CH-NH}$ coupling of this magnitude.[24]

The two geometrical isomers of **3** are present in a ratio of ca. 1:1.4 ($C_{3h}$:$C_s$) in $CDCl_3$ and 1:1.5 in DMSO-$d_6$. Statistically, a random orientation of the three enamines would generate a

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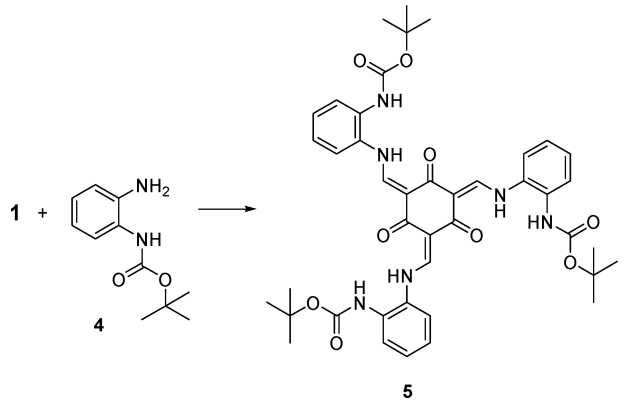
**SCHEME 3. Synthesis of TSAN 5**




ratio of 1:3 for these isomers. This indicates that the molecule favors the more symmetrical isomer that leads to hydrogen-bonding to each ketone. Also, the difference in the two solvents is minor. The two geometrical isomers do not interconvert on the NMR time scale even when heated to 120 °C.

We reacted **1** with the $^t$BOC-protected *o*-phenylenediamine **4** (Scheme 3) to design TSANs equipped with an additional functional group available for hydrogen-bonding. The $^1$H NMR spectrum of **5** shows only broad singlets for the enamine and vinylic groups, in contrast to the spectra of other derivatives (e.g., **3**) that show multiple peaks corresponding to the two geometrical isomers at 12.5−13.5 and 8.0−9.0 ppm (Figure 1).

The electrospray ionization mass spectrum (ESI-MS) of compound **5** (Supporting Information) shows the presence of not only the $[\mathbf{5} + H]^+$ ion but also significant quantities of the $[\mathbf{5}_2 + H]^+$ species, suggesting the formation of a dimer in solution. To confirm the dimeric structure of **5**, crystals suitable for SCXRD were obtained from slow evaporation of a solution of **5** in 1:1 dichloromethane/hexanes. The molecular structure of **5** is shown in Figure 2 clearly indicating the formation of a capsule-type dimer.

In the structure, two molecules of **5** form a self-complementary hydrogen-bonded dimer. Six hydrogen bonds between the NH$^t$Boc groups and the carbonyl groups of the central ring hold the dimer together. The presence of just one isomer in solution can be explained by the fact that only isomers with $C_{3h}$ symmetry are able to form the thermodynamically favored dimeric aggregates. The $^1$H NMR spectrum is consistent with the high ($C_3$) symmetry afforded by a dimer rather than a larger aggregate.

In $CDCl_3$, there is no evidence of monomeric compound **5**; only a single geometric isomer is present and the NH peaks are broad in the $^1$H NMR spectrum. In DMSO-$d_6$, the molecule has fully dissociated and only sharp peaks are present, showing both the $C_{3h}$ and $C_s$ isomers, with clear *J*-coupling between the vinylic CH and the NH groups. Interestingly, the ratio of $C_{3h}$:$C_s$ isomers in DMSO-$d_6$ is 1.7:1, showing that the $C_{3h}$ isomer is strongly biased over the $C_s$ isomer compared with statistical expectation. The $C_{3h}$ geometry minimizes steric interactions between the bulky $^t$BOC-*o*-phenylenediamine substituents present in compound **5**.

When **5** in $CDCl_3$ (ca. 6.6 mM) was titrated with DMSO-$d_6$, dissociation of the dimer was only evident when the solvent contained ca. 15% (v/v) DMSO-$d_6$ or greater. Using a solvent mixture of 1:5 DMSO-$d_6$/$CDCl_3$ and using the NH peaks to distinguish the $C_s$ isomer (monomeric) from the $C_{3h}$ isomer (monomeric and dimeric), we estimated an association constant

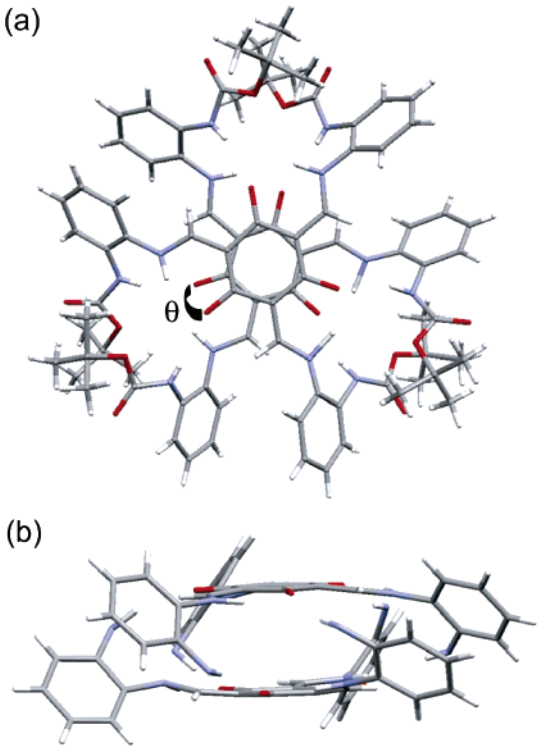



**FIGURE 2.** Structure of **5** as determined by SCXRD. The view of the dimer is shown from the top in (a), and the $^t$BOC protecting groups have been removed from the side view in (b) for clarity.

of 90 ± 50 $M^{-1}$.[25] This order of magnitude is realistic for a multiply hydrogen-bonded dimeric aggregate.[9f,26] As the $C_s$ isomer is never observed in $CDCl_3$, we can only provide a lower bounds on $K_{assoc}$ in $CDCl_3$. Assuming that the isomerization between the two isomers is facile in $CDCl_3$, that any trace of monomeric **5** is present in the same ratio in $CDCl_3$ as in DMSO-$d_6$ (i.e., 1.7:1 for $C_{3h}$:$C_s$ isomers), and that there is less than 2% of the $C_s$ isomer present at 5 mM in $CDCl_3$, the equilibrium constant for association ($K_{assoc}$) must be $>3 \times 10^4$ $M^{-1}$.

Variable-temperature $^1$H NMR experiments corroborated the existence of a dimer in solution (see Supporting Information for spectra). The $^1$H NMR spectrum of **5** is broad at room temperature. When the sample was heated to >60 °C (in $C_2D_2Cl_4$), the peaks became sharp and a mixture of the two isomers ($C_{3h}$ and $C_s$) was apparent. When the same sample was cooled (in $CD_2Cl_2$), the peaks became sharp at −20 °C and the major species present (>95%) was the $C_{3h}$ isomer as expected for the dimer. The $C_s$ isomer was not present, but a new product, which may be a larger aggregate, was also visible at low temperatures. These results indicate that below room temperature, only the $C_{3h}$ isomer is present, whereas at high temperature, the dimer dissociates to give a mixture of $C_{3h}$ and $C_s$ isomers. This dynamic monomer−dimer equilibrium is responsible for the broad peaks observed at room temperature.

In addition to the intermolecular hydrogen bonds, further stabilization of the dimer may originate from cofacial interactions of the central cyclohexanetrione cores. These rings are

(25) To obtain this number, samples were prepared in 1:5 (v/v) DMSO-$d_6$/$CDCl_3$ at various concentrations. $^1$H NMR spectra were obtained and the regions of interest (NH protons, 11.5−13.0 ppm) were integrated to determine the ratio of species present. This calculation included several assumptions, which are discussed in Supporting Information.

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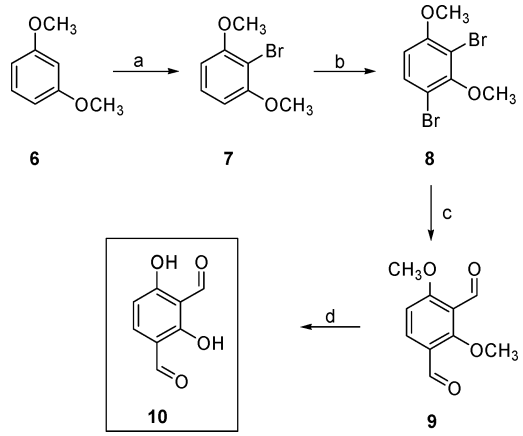
**SCHEME 4. Synthesis of Compound 10**[a]

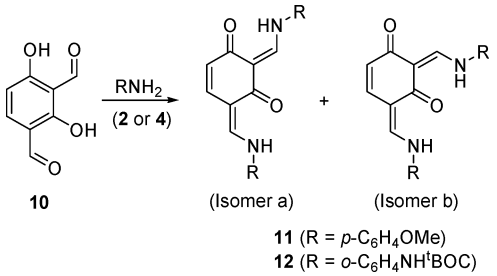



[a] Reagents and conditions: (a) $^n$BuLi/$C_2H_4Br_2$, 65%; (b) NBS/MeCN, 86%; (c) $^n$BuLi/DMF/$H^+$, 50%; (d) $BBr_3/CH_2Cl_2$, 81%.

coplanar and separated by only 3.35 Å in the solid state, close enough for significant $\pi-\pi$ interaction. The top ring is rotated 23.6° relative to the bottom ring as illustrated by the parameter $\theta$ in Figure 2a. The peripheral aromatic phenylenediamine rings may also participate in favorable $\pi-\pi$ interactions. Although this interaction is only weakly observed in the solid-state structure (closest interatomic separation of 3.6 Å), it may be more prominent in the solution state and enhance the overall stability of the dimer.

**BSANs.** By reducing the number of functional groups around the central ring, we felt that it might be possible to access molecular clefts.[5a,b,27] Compound **10** featuring two hydroxyl and two formyl groups is a good candidate for building clefts. Although there are reports of compound **10**,[28] there is only one previous report of an aniline derivative of **10**, but the authors claimed that the bis(imine) form was present.[29] Moreover, Schiff base condensations of amines with **10** have been claimed to afford imines in several patents without supporting evidence.[30] DFT calculations of the product formed by reacting aniline with **10** indicated that it should also tautomerize to the keto-enamine (NH) form. We established an improved synthetic procedure to **10** in four steps, starting from 1,3-dimethoxybenzene (Scheme 4). Key to the procedure is the selective bromination of **7** and the double metal−halogen exchange of **8**. Compound **10** was isolated in multigram quantities in 23% overall yield.

**SCHEME 5. Synthesis of Compounds 11 and 12**




The reaction of **10** with aniline derivatives (e.g., **2**, Scheme 5) afforded products that are predominantly in the keto-enamine tautomer and were also obtained as a mixture of two geometrical isomers (Figure 3). The $^1$H NMR spectrum of **11** shows the presence of two geometrical isomers (isomers a and b), with multiple peaks between $\delta$ 6.5−9.0 and 12.5−14.5 ppm. $^1$H−$^1$H COSY NMR spectra elucidated coupling between doublets in these two regions that could be assigned to the different isomers. As with the TSANs, there is significant coupling ($^3J_{HH}$ ≈12−13 Hz) between the vinylic and amine protons, indicating that the protons are localized on the N atoms (keto-enamine form) and exchange is slow on the NMR time scale. The $^{13}$C NMR spectrum of **11** showed the carbonyl resonances at ca. 187 ppm, characteristic of the keto isomer.

The two geometrical isomers of **11** are present in a ca. 3:1 ratio (isomer a:isomer b) in $CDCl_3$. Assuming the two enamines in **11** could be in any geometrical isomer that ensured both amines were hydrogen-bonded to ketones, these isomers should be present in a 1:1 ratio. The isomer that involves hydrogen-bonding to both ketones (isomer a) is strongly favored in solution. In DMSO-$d_6$, the ratio of these two isomers is ca. 2.3:1, suggesting less bias toward isomer a in this solvent. The presence of water in the NMR solvent may also affect the equilibrium by hydrogen-bonding to **11**.

The reaction of **10** with monoprotected *N*-$^t$BOC-*o*-phenylenediamine **4** afforded a product **12** with a significantly different $^1$H NMR spectrum, indicating the presence of a single geometrical isomer in solution (Figure 4). Crystals of **12** suitable for X-ray diffraction were obtained from $CHCl_3$/MeCN. Although a weak diffraction pattern was obtained, the structure was solved to give reliable information about the extended structure and some information about the bonding in the structure. The molecular structure shown in Figure 5a (one of the two molecules in the asymmetric unit) confirms that **12** is locked exclusively in the keto-enamine (NH) form in the solid state. The central ring is nearly flat, but highly distorted from a typical benzene ring. One bond length (HC═CH; C45 to C46) is 1.326(15) Å and typical of a vinylic group, whereas the other four bond lengths range from 1.403(15) to 1.455(15) Å, more typical of single bonds. Furthermore, the C═O length in the central ring of this molecule is 1.271(12)−1.284(12) Å, which is consistent with a ketone rather than a phenol. An elongated C−N bond length relative to an imine further confirms the keto-enamine form for the molecule in the solid state. A second molecule of **12** in the asymmetric unit is similarly locked in the keto-enamine form, though the molecule is slightly more distorted about one amine. The molecular structure of **12** is consistent with the calculated structure for the keto-enamine form, which will be discussed later.

The presence of a single geometrical isomer in BSAN **12** ($^1$H NMR) is reminiscent of TSAN **5** and suggested the presence

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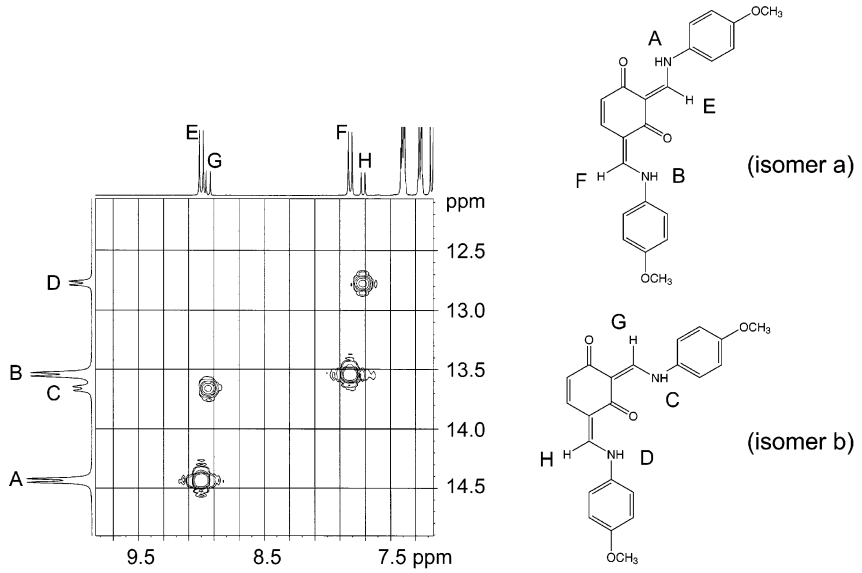



**FIGURE 3.** $^1$H−$^1$H COSY NMR spectrum of **11** showing coupling between vinylic and NH protons. At the right are the two structures evident in the $^1$H NMR spectrum.

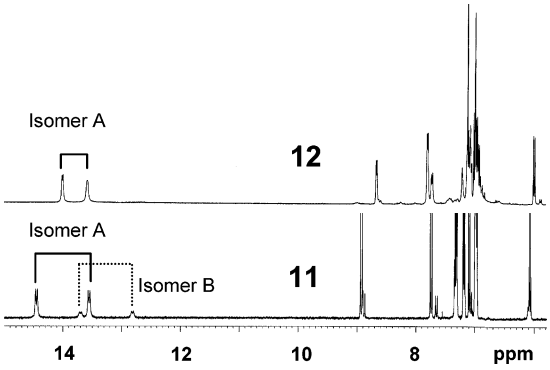



**FIGURE 4.** $^1$H NMR spectra of compounds **11** and **12** ($CDCl_3$, 300 MHz). The peaks at 12−15 ppm are the NH resonances.

of a dimer in solution. The simplicity of the NMR spectrum also corroborates a dimer rather than a more complex, less symmetrical aggregate. ESI-MS data provided additional evidence for the presence of a dimer in solution, showing both [**12** + Na]$^+$ and [**12**$_2$ + Na]$^+$ species in the mass spectrum (Supporting Information). When dissolved in DMSO-$d_6$, the $^1$H NMR spectrum indicates that **12** reverts to a mixture of isomers a and b in a ratio of 8.8:1. With the bulky *N*-$^t$BOC-*o*-phenylenediamine substituents, the less sterically encumbered geometry of isomer a is strongly preferred over isomer b. We believe that in $CDCl_3$, this molecule likely forms hydrogen-bonded dimers similar to those observed in **5**, but with only four hydrogen bonds holding the cleft together. A molecular model of the proposed dimer is shown in Figure 5b,c. In this structure, there is a cleft evident between the two central rings.

The stability of the cleft was probed by dilution experiments using NMR spectroscopy. Samples of **12** in $CDCl_3$ ranging from 560 $\mu$M to 19 mM showed no change and no evidence of dissociation. UV−vis spectra between $10^{-4}$ and $10^{-6}$ M showed no shifts in the absorption spectrum. The cleft in $CDCl_3$ (ca. 1.9 mM) was titrated with DMSO-$d_6$. Dissociation of the dimer was evident only at concentrations of >10% v/v DMSO-$d_6$. We wished to obtain association constants for the dimerization of **12** in solution, but peaks of the dimer could not be distinguished from those of the monomer. In addition, when the molecule dissociates, the equilibrium is affected by isomerization between the two isomers (a and b). If we assume that the isomerization between the two isomers is facile in $CDCl_3$, that any trace of monomeric **12** is present in the same ratio in $CDCl_3$ as in DMSO-$d_6$ (i.e., 8.8:1 for isomers a:b), and that there is less than 2% of isomer b present at 560 $\mu$M in $CDCl_3$, the equilibrium constant for association ($K_{assoc}$) must be $>10^4$ M$^{-1}$. We are unable to provide an upper bound on the stability constant of the dimer, but it could be much larger.

Although the molecule assembles into hydrogen-bonded dimers in solution, the solid-state structure shows that the molecules are organized into dimers that form an extended hydrogen-bonded structure, Figure 6. Each dimer is formed by a pair of nearly cofacial cyclohexenediketone rings of compound **12**, rotated about 120° relative to one another. The rings are 3.6(1) Å apart, indicating a weak $\pi-\pi$ interaction between the rings. Two hydrogen bonds between the NH$^t$BOC groups and the carbonyl groups of the central ring hold the dimers together. These are half of the hydrogen bonds that are likely present in the dimer in solution, as modeled in Figure 5b,c. Moreover, there are cofacial $\pi-\pi$ interactions present between two of the phenylenediamine substituents of the compound, with nearest interatomic distances of only ca. 3.4 Å.

Hydrogen bonds formed between the NH$^t$BOC groups not involved in stabilizing the cofacial dimer, and ketones bridge adjacent dimers in the solid state. This extended structure is depicted in Figure 6a. The solubility of the crystals in $CDCl_3$ or DMSO-$d_6$ indicate that the extended structure is easily disrupted.

Compound **10** is only one of five possible dihydroxydiformylbenzene isomers where the hydroxy/formyl groups are arranged in pairs around a single benzene ring, as in salicylaldehyde. To obtain information on how the position of the hydroxyl/formyl groups within the central ring affects the formation of the all keto-enamine (NH) form and possible dimerization, we reacted compounds **13**, **15**, and **17** with **4** (Scheme 6). $^1$H NMR spectra clearly indicated that all three products **14**, **16**, and **18** are present exclusively in the enol-imine (OH) form. This is not at all surprising for **16** and **18**,

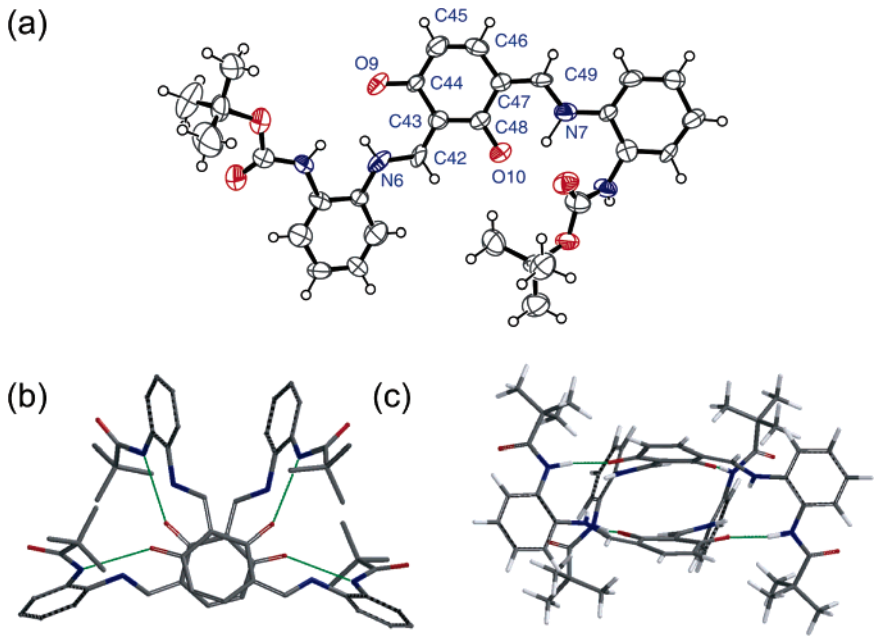



**FIGURE 5.** (a) Molecular structure of one molecule of **12** in the solid state (thermal ellipsoids at 50% probability). (b, c) Molecular model of a dimer of **12** as viewed from the top (b) and side (c) of the cleft showing hydrogen bonds (green). Hydrogen atoms have been omitted from the model in (b) for clarity.

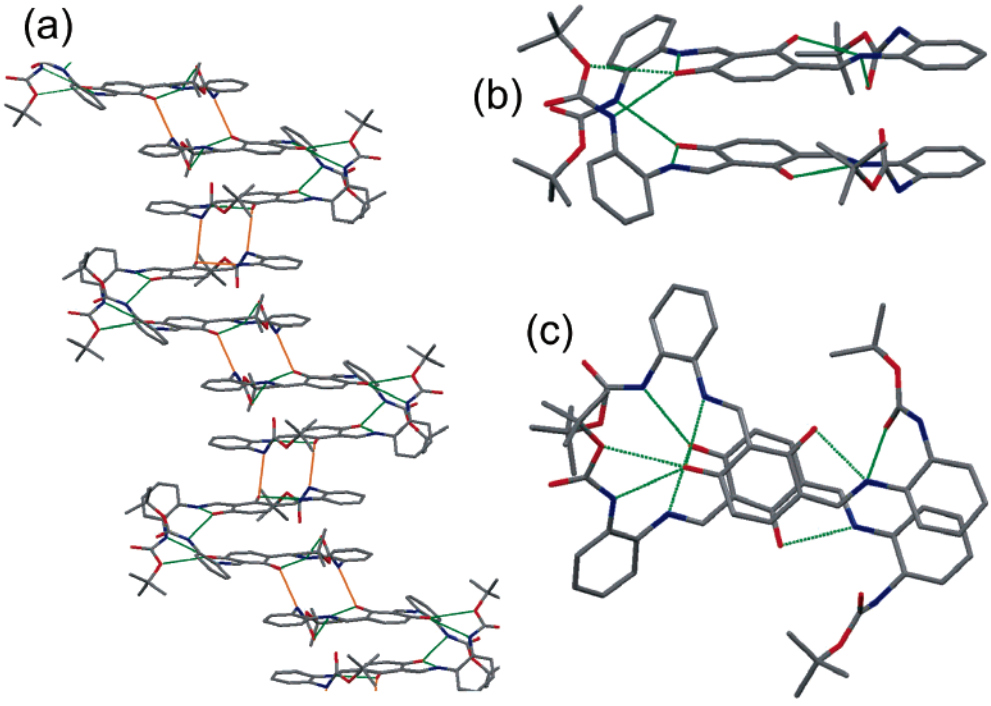
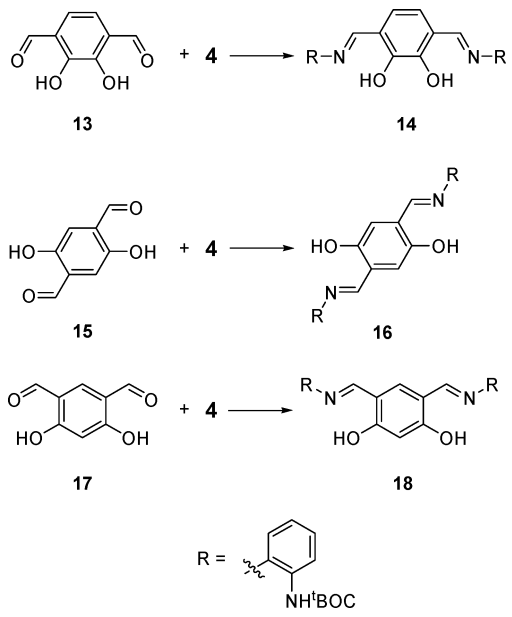



**FIGURE 6.** (a) SCXRD structure of ladder polymer formed by **12** with intermolecular hydrogen bonds shown in orange. (b, c) Face-to-face stacking of **12** in the solid state (from SCXRD) with inter-dimer hydrogen bonds shown in green. Hydrogen atoms have been omitted for clarity.

since tautomerization of the two enol-imine groups would leave free radicals on two of the CH groups of the central ring. The lack of tautomerization observed for **14**, however, was unexpected on the basis of our results with **10** and will be discussed later.

In compounds **5** and **12**, the presence of the $^{t}$BOC-protected amine is important for generating hydrogen-bonded dimers or extended structures. To obtain information on how the position of the amino substituents affects dimerization, we reacted **1** and **10** with *N*-$^{t}$BOC-*m*-phenylenediamine **19** in place of the ortho derivative **4** to afford compounds **20** and **21**, respectively (Scheme 7). The $^{1}$H NMR spectra of **20** and **21** clearly indicate that no aggregation occurs when **1** and **10** are reacted with the *meta*-derivative instead of the ortho derivative. Both compounds show the characteristic peak pattern that derives from the presence of two geometrical isomers locked in the keto-enamine form. Presumably this geometry does not permit effective interaction between the NH groups and the carbonyl function-

**SCHEME 6. Synthesis of Compounds 14, 16, and 18**




alities as the *m*-phenylenediamine ring must undergo excessive twisting to position the NH groups in close proximity of the carbonyl groups in its partner ring.

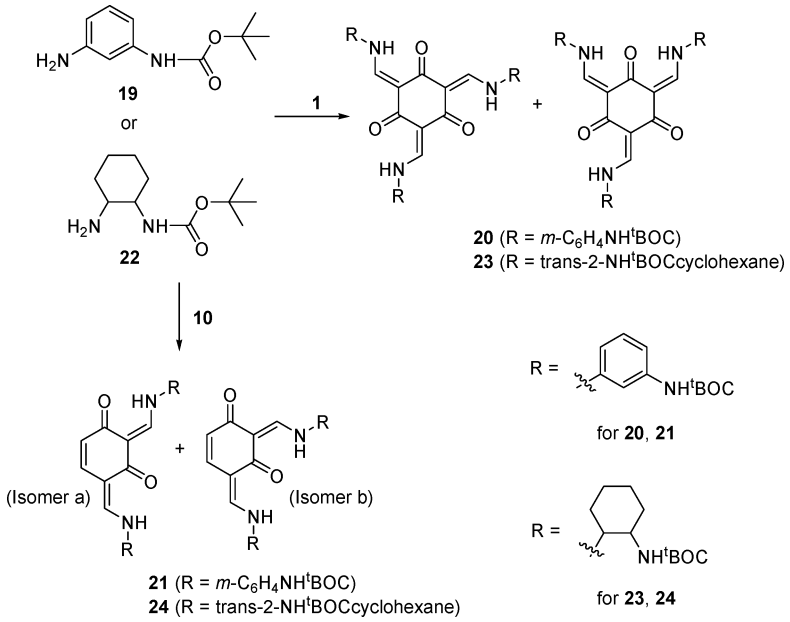
To date, all of the keto-enamine tautomers we have investigated have involved aniline derivatives. Compounds **1** and **10** were reacted with a racemic mixture of *N*-$^t$BOC-*trans*-1,2-diaminocyclohexane **22** to give compounds **23** and **24**, respectively (Scheme 7). These compounds with aliphatic substituents are also locked in the keto-enamine form, demonstrating that the aromaticity of the substituents is not a requirement for stabilization of this tautomer. However, both **23** and **24** are found as a mixture of two geometrical isomers (ca. 1.6:1 for $C_{3h}$:$C_s$ isomer in **23**, 1.3:1 for isomer a: isomer b in **24**) and show no evidence for aggregation. Since the starting compound **22** is present as a racemic mixture, the products **23** and **24** contain multiple isomers that may not interlock well. In addition, the steric bulk of accommodating four or six cyclohexane moieties around the core may inhibit dimerization.

These results show that the geometry of the $^t$BOC-protected diamines is important for facilitating dimerization in these molecules. If the $^t$BOC-protected amine and the free amine could be separated further, keeping the geometry appropriate for dimerization, then capsules or clefts with adjustable interior cavity sizes may be obtainable. In an effort to extend the space between the central rings of the clefts, we synthesized *N*-$^t$BOC-1,8-diaminonaphthalene **25** and reacted it with compound **10** (Scheme 8). ESI-MS indicated the mass expected for the condensation product, but the $^1$H NMR spectrum was inadequate to confirm the product's identity. Single crystals suitable for X-ray diffraction were obtained from a mixture of dichloromethane and hexanes. The solid-state data (Figure 7) showed that **26** does not form the anticipated keto-enamine (NH) form. Surprisingly, the structure revealed the formation of a perimidine derivative, arising presumably via imine formation followed by nucleophilic substitution from the NH$^t$BOC amide, and finally proton transfer. The second aldehyde reacted with the diamine to yield a regular imine-phenol (OH) form. Perimidine formation at this imine may be hindered by steric crowding. In solution, we only observe the ring-closed perimidine, not the ring-opened chain structure.[31]

The central rings of compounds **12** and **26** are both derived from compound **10**. In compound **12**, both hydroxyl/formyl pairs have tautomerized to the keto-enamine form. This compound shows C−C, C−O, and C−N bond lengths that are consistent with the keto-enamine form. In compound **26**, on the other hand, the structure shows that neither hydroxyl/formyl pair have tautomerized to the keto-enamine form. In this case, the perimidine formed prevents the one hydroxy/formyl pair from tautomerizing, and the second pair does not tautomerize either. The C−O, C−C, and C−N bond lengths of the central ring in **26** are consistent with the enol-imine tautomer. It is interesting that we have characterized the central core of **12** and **26** in both the keto and enol forms.

Compounds **3** and **5** may be classified as hetero[6]radialenes.[32] These molecules possess six sp$^2$ hybridized carbon atoms in a

**SCHEME 7. Synthesis of Compounds 20, 21, 23, and 24**



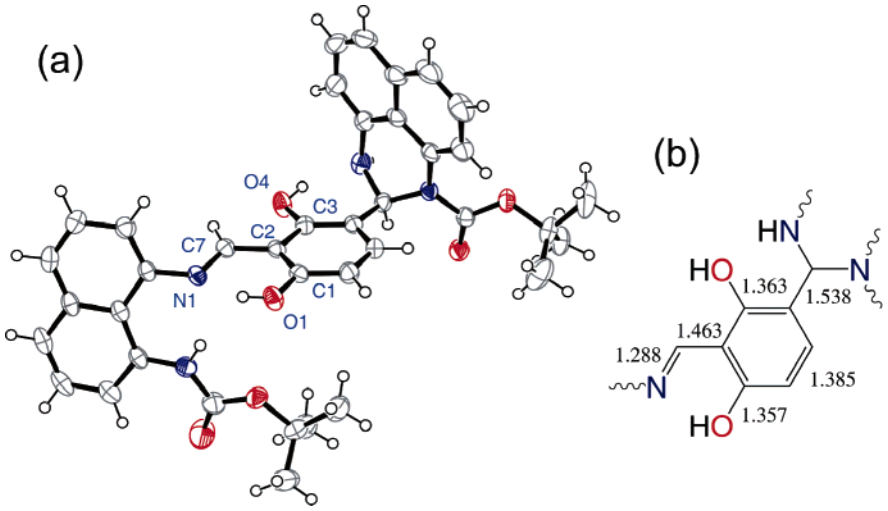
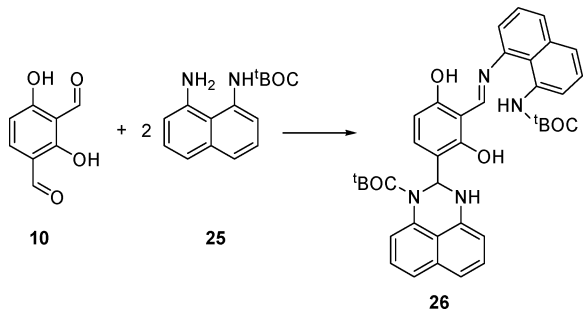



**FIGURE 7.** (a) Solid-state structure of compound **26** (thermal ellipsoids shown at 50% probability). (b) Schematic of the central ring in **26** and bond lengths measured by SCXRD. ESDs are 0.003−0.004 Å for the bond lengths shown.

**SCHEME 8. Synthesis of Compound 26**




cyclic structure. Previous examples of 1,3,5-trisoxo[6]radialenes have been limited to a few examples with sulfur substituents.[33,34] Although compounds **11** and **12** are not technically radialenes, they have a central 2,3-dimethylidenecyclohex-5-ene-1,3-one that has only been observed in a few examples with ethylenedithiol substituents.[33]

**Calculations.** Computation of hydroxynaphthaldehyde anils, azo compounds, and related systems has provided important information about tautomerization in these compounds.[35] In general, enaminones (e.g., 4-methylamino-3-buten-2-one) are found in their keto-enamine (NH) form.[36] When they form part of a benzene ring, as in *N*-salicylideneanilines, the molecules are present in the enol-imine (OH) tautomeric form. In this case, tautomerization from the enol-imine to the keto-enamine form would result in the unfavorable loss of aromaticity. Only larger aromatic rings (e.g., phenanthrene, naphthalene) can stabilize the keto-enamine form. There have been reports of *N*-salicylideneanilines existing as mixtures of NH and OH forms, but the structural characterization of a purely NH form has been difficult.[16−19] We have found that the condensation of amines with both **1** and **10** afford compounds that are exclusively in the keto-enamine (NH) form, whereas condensation of amines with **13**, **15**, and **17** affords only the enol-imine (OH) tautomers. In an effort to rationalize the stability of the keto-enamine form and to compare the structural features of the two tautomers, we have carried out the first ab initio and semiempirical calculations on a series of model compounds **27**−**33** shown in Figures 8 and 9. In the model compounds, the group attached to the

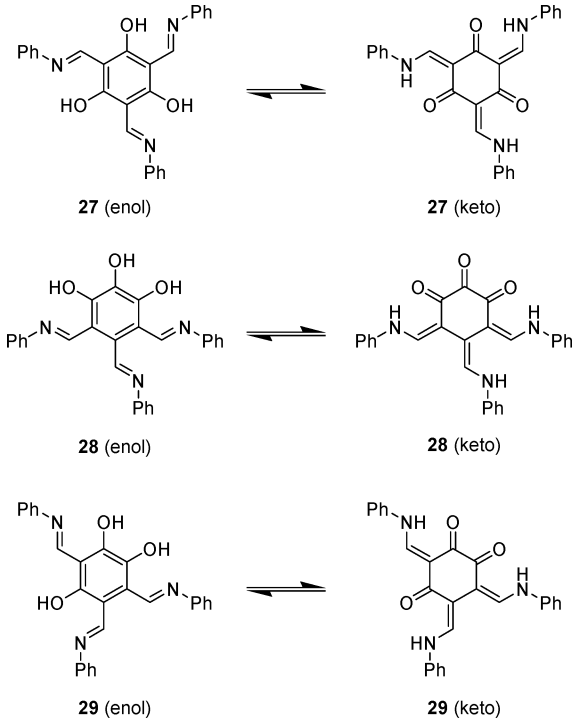



**FIGURE 8.** Structures of model compounds **27**−**29** used in the calculations of the TSANs.

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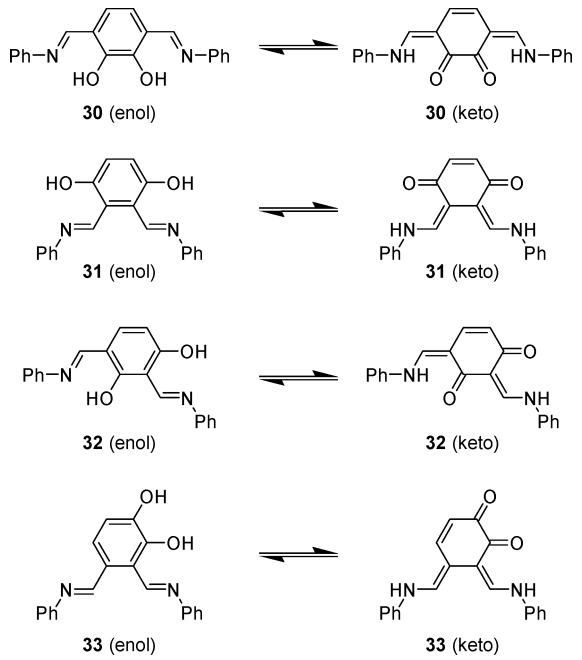


**FIGURE 9.** Structures of model compounds **30**−**33** used in the calculations of the BSANs.

nitrogen atoms was truncated to a phenyl group; this abbreviated structure is a sensible analogue of the methoxyaniline derivatives **3** and **11**. Compounds **27**−**29** (Figure 8) represent all of the possible tris(*N*-salicylideneaniline) structural isomers generated by the condensation of trihydroxytriformylbenzene and aniline. Model compounds **30**−**33** (Figure 9) are the only possible salicylaldimine isomers arising from the condensation of aniline with dihydroxydiformylbenzene, where the two aromatic CH substituents are arranged adjacent (ortho) to one another (i.e., 1,2,3,4-tetrasubstitution). The tautomerization to the bis(keto-enamine) form would only be plausible with these arrangements since other arrangements (e.g., 1,2,4,5-tetrasubstitution) would result in two free radicals on the central ring in the keto-enamine form. Calculation of one of these isomers indicated that this would be very high in energy and thus unlikely to form.

Conformations were selected that maximized O···H···N hydrogen-bonding. In the cases of the keto-enamine forms of compounds **27**, **29**, and **32**, the conformation was selected that utilized all of the oxygen atoms available for hydrogen-bonding. Although there are other geometrical isomers available where one ketone is involved in two hydrogen bonds (as in isomer b of compound **11**), these were ignored for the purpose of calculations. In each model compound, the minimum energy geometries of both the keto and enol tautomers were determined using B3LYP with the 6-31G* basis set. Calculations were completed starting with different relative orientations of the phenyl rings until the lowest energy structure was identified. Single point calculations were then performed on the energy-minimized structures using B3LYP with the 6-31G** basis set. Geometry optimization calculations were also performed starting with the geometries obtained from B3LYP/6-31G* using AM1 and PM3 to evaluate the abilities of these semiempirical methods to predict the most stable tautomer. The results of the calculations are summarized in Tables 1 and 2.

To confirm that this level (B3LYP/6-31G*) was reasonable for approximating the geometry of the tautomers, geometry optimizations were performed on compounds **27** and **32** with the 6-31G** basis set. The structures calculated with the larger basis set were almost identical to those obtained with the 6-31G* basis set, with bond lengths varying by only 0.001−0.002 Å.

**TSANs.** For the compounds containing three OH and three imine groups on the benzene ring, compounds **27** and **29** are predicted to exhibit keto-enamines that are more stable than the enol-imine isomers in the gas phase. In these compounds, three OH···N interactions in the enol-imine form are replaced with three NH···O interactions in the keto-enamine tautomer. In compound **28**, however, where the three OH groups are adjacent to one another, ab initio calculations predict that the enol-imine isomer is most stable. In this case one OH···O and two OH···N hydrogen-bonding interactions in the enol-imine form are replaced by only two NH···O interactions in the keto-enamine form. This loss of hydrogen-bonding in the keto form, as well as steric interactions of the three adjacent enamine groups, is likely responsible for the destabilization of the keto-enamine form. Semiempirical methods agree with the ab initio results for **27** and **29** but predict the keto-enamine tautomer to be most stable for **28**.

We are particularly interested in the predicted structure for compound **27**, since it is similar to compound **5**. The enol-imine (OH) form of compound **27** is predicted to have a flat interior shared by the imine groups and the central benzene ring, with

**TABLE 1. Calculated Energies of Formation for TSANs 27−29**

| compd | $E_{enol}$[a] (Hartree) | $E_{keto}$[a] (Hartree) | $\Delta E_{(enol-keto)}$[a] (kcal/mol) | $\Delta E_{(enol-keto)}$[b] (kcal/mol) | $\Delta E$ (AM1)[c] (kcal/mol) | $\Delta E$ (PM3)[c] (kcal/mol) |
|---|---|---|---|---|---|---|
| **27** | −1431.513081 | −1431.534675 | 13.55 | 18.12 | 22.94 | 5.97 |
| **28** | −1431.470838 | −1431.452264 | −11.66 | −7.5 | 9.29 | 3.41 |
| **29** | −1431.486756 | −1431.497803 | 6.93 | 11.00 | 17.00 | 4.67 |

[a] Single point determination using B3LYP with 6-31G** basis set on B3LYP/6-31G* geometry. [b] B3LYP/6-31G* basis set. [c] Geometry optimized beginning from B3LYP/6-31G* geometry.

**TABLE 2. Calculated Energies of Formation for BSANs 30−33**

| compd | $E_{enol}$[a] (Hartree) | $E_{keto}$[a] (Hartree) | $\Delta E_{(enol-keto)}$[a] (kcal/mol) | $\Delta E_{(enol-keto)}$[b] (kcal/mol) | $\Delta E$ (AM1)[c] (kcal/mol) | $\Delta E$ (PM3)[c] (kcal/mol) |
|---|---|---|---|---|---|---|
| **30** | −1031.744646 | −1031.739779 | −3.05 | −0.67 | 4.77 | −4.37 |
| **31** | −1031.741870 | −1031.738826 | −1.91 | 0.71 | 3.99 | −5.00 |
| **32** | −1031.757359 | −1031.761948 | 2.88 | 5.46 | 7.80 | −2.52 |
| **33** | −1031.738162 | −1031.717439 | −13.00 | −10.32 | −4.51 | −7.16 |

[a] Single point determination using B3LYP with 6-31G** basis set on B3LYP/6-31G* geometry. [b] B3LYP/6-31G* basis set. [c] Geometry optimized beginning from B3LYP/6-31G* geometry.

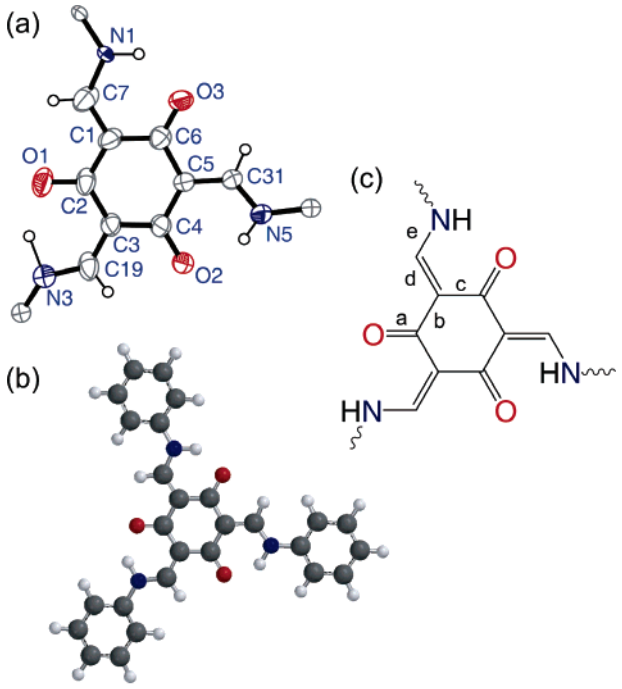


**FIGURE 10.** (a) Structure of the core of compound **5** as determined by SCXRD. Thermal ellipsoids are shown at 50% probability. The substituents have been truncated at the *ipso*-carbon atom of the phenyl ring to emphasize the structure of the core. Only one position of N1 and N3 are shown, with disordered fragments omitted for clarity. (b) Calculated energy-minimized structure (B3LYP/6-31G**) of the keto-enamine form of compound **27**. (c) Illustration of the core of **5** and **27** with key bond lengths identified for Table 3.

**TABLE 3. Bond Lengths Determined for 5 (from SCXRD) and 27 (Calculation)**

| bond[a] | | **5** (XRD)[b] (Å) | **27** keto (DFT)[c] (Å) | **27** enol (DFT)[c] (Å) |
|---|---|---|---|---|
| a | C═O | 1.256(8) | 1.257 | 1.327 |
| b | C−C | 1.45(2) | 1.466 | 1.419 |
| c | C−C | 1.45(1) | 1.460 | 1.422 |
| d | C═C | 1.38(1) | 1.386 | 1.440 |
| e | C−N | 1.34(6) | 1.337 | 1.299 |

[a] See Figure 10. [b] $T = -100$ °C. [c] B3LYP/6-31G** geometry optimized structure.

the three phenyl substituents in a propeller orientation (dihedral angle of ca. 31−34° between imine and phenyl ring). In the more stable keto-enamine (NH) form, however, the molecule is predicted to be flat, enabling delocalization of the electrons on the nitrogen atoms into the conjugated system containing the ketones (geometry optimization with 6-31G** basis set revealed a slight (1−3°) torsion of the peripheral phenyl rings). A structure of the molecule and its relevant bond lengths are shown in Figure 10. The bond lengths calculated for the keto-enamine structure agree with those determined by X-ray diffraction (Table 3), verifying that TSAN **5** is in the keto-enamine form.

The computed enol-imine form of compound **29** is similar in geometry to compound **27**, with a flat interior and propeller orientation of the phenyl substituents. In the keto-enamine form, however, steric interactions between the adjacent enamine groups lead to twisting of the central ring and probably reduce the degree of conjugation. As a consequence, the keto-enamine form is only slightly more stable than the enol-imine tautomer. In compound **28**, where the keto-enamine form is predicted to be the least stable tautomer, steric interactions of the three enamine groups lead to a large distortion of the central ring from planarity in the calculated structure for the keto-enamine form.

**BSANs.** Table 2 lists the energies of the structures calculated for the BSANs **30**−**33**. In TSANs **27** and **29**, the stabilization afforded from the formation of three keto-enamine tautomers was sufficient to overcome the resonance stabilization of the aromatic ring. In the BSANs, it is unclear whether the stabilization of only two groups tautomerizing is sufficient to overcome the stabilization of the aromatic ring. Both ab initio and semiempirical methods predict that compound **33** will be most stable in the enol-imine (OH) tautomer. In this case, steric interactions of the aniline substituents as well as the loss of a hydrogen bond in the keto form render the enol-imine tautomer more stable. Steric interactions between the rigid enamine groups in compound **31** also destabilize the keto form.

In our studies of BSANs, we were most surprised that products formed by the condensation of aniline derivatives with 1,3-dihydroxy-2,4-diformylbenzene **10** (i.e., compounds **11**, **12**, **21**) gave products locked in the keto-enamine (NH) form, whereas products obtained from the condensation of aniline derivatives with 1,2-dihydroxy-3,6-diformylbenzene **13** (i.e., compound **14**) were locked in the enol-imine (OH) form. In both cases, there is no decrease in the number of hydrogen bonds between the keto-enamine and enol-imine forms, nor is there significant steric interaction between the bulky peripheral phenyl rings. Ab initio calculations agree with the experimental observations and correctly predict the most stable tautomer for compounds **30** and **32**.

The enhanced stability of the keto-enamine tautomer in **32** versus **30** can be rationalized by considering the resonance structures of the molecule. Stabilization by resonance-assisted hydrogen-bonding is facilitated by ortho/para arrangement of the keto groups to the enamines in **32**.[37] There are two additional resonance structures that contribute in the case of the keto-form of **32**. This is illustrated in Figure 11.

We were hopeful that computation would allow us to unequivocally assign the structures obtained for compounds **12** and **26** to the keto-enamine and enol-imine form, respectively. The isolation and structural characterization of two different tautomers is useful for determining the tautomeric form and for evaluating the accuracy of our computations. The enol-imine form of compound **32** is predicted to have a flat interior shared by the imine groups and the central benzene ring, with the two phenyl substituents twisted with a dihedral angle of ca. 34−36° between imine and phenyl ring. In the more stable keto-enamine form, however, the molecule is predicted to be flat, enabling delocalization of the electrons on the nitrogen atoms into the conjugated system containing the ketones. A structure of the molecule and its relevant bond lengths are shown in Figure 12. Although the figures of merit for the structure determined from SCXRD are not outstanding due to disorder, the bond lengths calculated for the keto-enamine structure correspond quite well to those determined by X-ray diffraction (there are two independent molecules of **12** in the asymmetric unit), Table 4. Most importantly, the C═O bond lengths range

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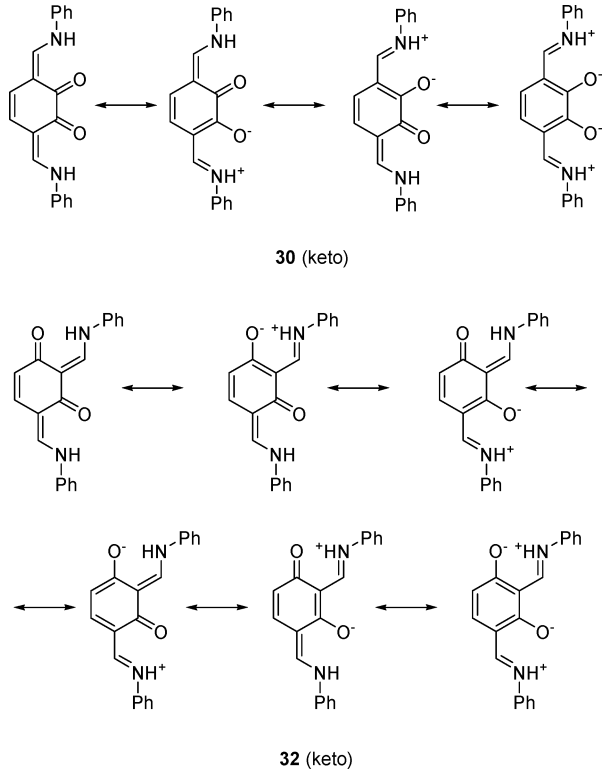


**FIGURE 11.** Resonance stabilization of the keto-enamine form of compounds **30** and **32**.

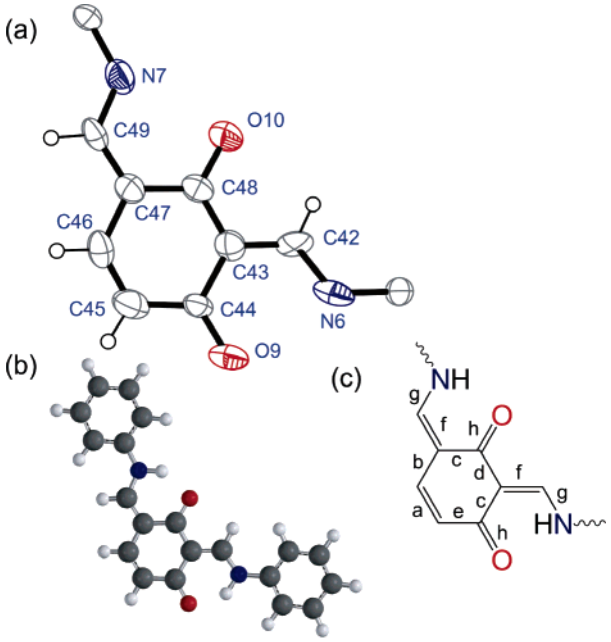


**FIGURE 12.** (a) Structure of the core of compound **12** (one of two molecules in the asymmetric unit) as determined by SCXRD. Thermal ellipsoids are shown at 50% probability. The substituents have been truncated at the *ipso*-carbon atom of the phenyl ring to emphasize the structure of the core. (b) Calculated energy-minimized structure (B3LYP/6-31G**) of the keto-enamine form of compound **32**. (c) Illustration of the core of **12** and **32** with key bond lengths identified for Table 4.

from 1.258(12) to 1.284(12) Å, which are as expected for the keto-enamine tautomer. Thus, BSAN **12** is indeed present in the keto-enamine form, consistent with NMR solution data. The bond lengths of the core in compound **26** are also included, recognizing that the perimidine substituent is not an imine and does not have the same extent of conjugation. Nonetheless, the bond lengths determined for compound **26** agree closely with those calculated for the enol-imine form of a salicylideneaniline. The C−O bond lengths are characteristic of single bonds, while the C═N bond length is consistent with an imine.

**TABLE 4. Bond Lengths Determined for 12 (SCXRD), 26 (SCXRD), and 32 (Calculation)**

| bond[a] | | **12** (XRD)[b] (Å) | **32** keto (DFT)[c] (Å) | **32** enol (DFT)[c] (Å) | **26** (XRD)[b] (Å) |
|---|---|---|---|---|---|
| a | C═C | 1.33(2) | 1.357 | 1.379 | 1.385(4) |
| b | C−C | 1.44(1) | 1.439 | 1.412 | 1.401(4) |
| c | C−C | 1.45(3) | 1.467, 1.469 | 1.424, 1.422 | 1.407(6) |
| d | C−C | 1.42(2) | 1.461 | 1.416 | 1.418(3) |
| e | C−C | 1.43(2) | 1.456 | 1.410 | 1.393(4) |
| f | C═C | 1.39(2) | 1.385, 1.387 | 1.446, 1.441 | 1.463(3) |
| g | C−N | 1.32(2) | 1.334, 1.342 | 1.296, 1.297 | 1.288(3) |
| h | C═O | 1.27(1) | 1.256, 1.259 | 1.330, 1.335 | 1.360(4) |

[a] See Figure 12. [b] $T = -100$ °C. [c] B3LYP/6-31G** geometry optimized structure.

The DFT methods were useful to predict the most stable tautomer of the BSANs and TSANs and to estimate their expected geometries. The use of B3LYP/6-31G* with a 6-31G** single point calculation is adequate to correctly predict the most stable isomer for the BSANs and TSANs we prepared. The only questionable result is that for compound **31**. In this case, B3LYP/6-31G* predicted that the keto-enamine tautomer would be most stable, while a single point calculation with 6-31G** predicted that the enol-imine tautomer was more stable. We believe the 6-31G** result as the tautomers of this compound should show stability comparable to those of compound **30**. Semiempirical methods, which are substantially faster, were also evaluated. PM3 did not accurately predict the most stable tautomer in most cases, while AM1 methods usually agreed with the DFT/experimental results. AM1 has previously shown good utility in predicting the stability of salicylaldimine tautomers[34b] but has not been used to examine BSANs or TSANs.

Our calculations indicate that compound **31**, if it could be synthesized, may be a good target for developing a bistable molecular switch. In this compound, the energy difference between the keto and enol tautomers is small so it may be possible to utilize this compound or related BSANs for photoswitching. We hope that others will be inspired to develop synthetic routes to these novel compounds.

## Conclusions

We have discovered new tris(*N*-salicylaldimine)s and bis(*N*-salicylaldimine)s that undergo tautomerization to very stable keto-enamine tautomers. We have structurally characterized the keto-enamine form of two of these compounds, as well as an enol-imine form of another. Calculations show that the tautomerization is general and is stabilized by resonance between the enamine and keto groups. The hydrogen-bonding abilities of TSANs and BSANs make them good candidates for the formation of dimeric capsules and clefts, respectively. We have structurally characterized a dimeric capsule-type assembly and an extended network formed by BSANs. Further studies of aggregation in BSANs and TSANs are underway.

## Experimental Section

**Synthesis of 1,3-Dimethoxy-2,4-diformylbenzene (9).** Under a nitrogen atmosphere 1,3-dibromo-2,4-dimethoxybenzene (27.5 g,

93 mmol) was dissolved in 600 mL of dry diethyl ether and cooled to 0 °C. *n*-Butyllithium (175 mL of a 1.6 M solution in hexane, 280 mmol) was added over a period of 10 min and the resulting yellow, milky mixture was stirred for 30 min. Anhydrous DMF (15.5 mL, 200 mmol) was then added dropwise and the suspension was stirred for an additional 30 min at 0 °C before being warmed to room temperature. The reaction mixture was poured into 1 L of water, followed by the addition of 400 mL of concentrated HCl. The resulting two phases were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting brown solid was recrystallized from toluene yielding **9** as colorless needles (9 g, 46 mmol, 50%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.44 (s, 1H), 10.26 (s, 1H), 8.05 (d, 1H, $J$ = 9 Hz), 6.85 (d, 1H, $J$ = 9 Hz), 3.98 (s, 6H) ppm; $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 188.3, 187.9, 167.1, 165.9, 135.6, 123.4, 118.6, 108.1, 65.7, 56.8 ppm; MS (EI, 70 eV) *m*/*z* 194 ($M^+$); IR $\nu$ (KBr) = 3459, 2887, 1676, 1579, 1483, 1454, 1382, 1277, 1249, 1217, 1181, 1096, 947, 802, 734, 545 cm$^{-1}$; mp = 98−99 °C; HRMS-EI ($M^+$) calcd for $C_{10}H_{10}O_4$ 194.0579, found 194.0577. Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85, H, 5.19. Found: C, 61.87, H, 5.19.

**Synthesis of 1,3-Dihydroxy-2,4-diformylbenzene (10).** Under a nitrogen atmosphere 1,3-dimethoxy-2,4-diformylbenzene (5 g, 25.8 mmol) was dissolved in 100 mL of dry $CH_2Cl_2$ and cooled to 0 °C. To this solution was added $BBr_3$ (14.6 mL, 154 mmol), resulting in a color change from pale yellow to red. After stirring at 0 °C for 1 h the ice bath was removed and the solution was stirred at room temperature overnight. The solution was poured onto 400 mL of ice and the two phases were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL) and the combined organic layers were dried over $MgSO_4$. Solvent was removed under vacuum and the obtained red solid was purified by flash chromatography (silica, $CH_2Cl_2$) yielding **10** as a white powder (3.5 g, 21 mmol, 81%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.63 (s, 1H), 12.53 (s, 1H), 10.38 (s, 1 H), 9.69 (s, 1H), 7.63 (d, 1H, $J$ = 9 Hz), 6.54 (d, 1H, $J$ = 9 Hz) ppm; $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 194.5, 193.6, 169.6, 167.3, 141.8, 113.6, 110.2, 109.4 ppm; MS (EI, 70 eV) *m*/*z* 166 ($M^+$); IR $\nu$ (KBr) = 3439, 3096, 2895, 1640, 1599, 1483, 1410, 1386, 1306, 1257, 1225, 1181, 1084, 939, 831, 750, 670, 617, 577, 497 cm$^{-1}$; mp = 127−128 °C; HRMS-EI ($M^+$) calcd for $C_8H_6O_4$ 166.0266, found 166.0266. Anal. Calcd for $C_8H_6O_4$: C, 57.84, H, 3.64. Found: C, 57.74, H, 3.64.

**Synthesis of 11**. To a solution of **10** (0.1 g, 0.6 mmol) in 50 mL of ethanol was added 4-methoxyaniline (**2**) (0.246 g, 2 mmol) in 20 mL of ethanol and the solution was stirred at reflux overnight. The solution was cooled to room temperature and the solvent was removed under reduced pressure. The remaining yellow film was dissolved in THF and precipitated from hexanes. The precipitate was collected by filtration, washed with hexanes and dried under vacuum to give 0.129 g (0.3 mmol, 57%) of compound **11** as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 14.33 (d, 1H, $J$ = 12 Hz, C═CNH of isomer a), 13.56 (d, 1H, $J$ = 13 Hz, C═CNH of isomer b), 13.45 (d, 1H, $J$ = 12 Hz, C═CNH of isomer a), 12.67 (d, 1H, $J$ = 12.5 Hz, C═CNH of isomer b), 8.78 (d, 1H, $J$ = 12.5 Hz, HC−N of isomer a), 8.72 (d, 1H, $J$ = 13.5 Hz, HC−N of isomer b), 7.61 (d, 1H, $J$ = 12 Hz, HC−N of isomer a), 7.51 (d, 1H, $J$ = 12.5 Hz, HC−N of isomer b), 7.24−6.83 (m, 18H), 5.96 (d, 2H, $J$ = 9.5 Hz), 3.76 (s, 6H), 3.73 (s, 6H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 187.5, 187.3, 184.7, 159.6, 159.5, 158.7, 158.6, 153.3, 152.7, 150.2, 148.7, 142.8, 134.0, 133.9, 133.8, 133.4, 121.1, 120.9, 120.1, 119.9, 119.5, 118.0, 116.5, 111.7, 107.9, 107.5, 56.9 ppm; MS (EI, 70 eV) *m*/*z* 376 ($M^+$); IR $\nu$ (KBr) = 3463, 3052, 2944, 2827, 1648, 1615, 1579, 1527, 1511, 1450, 1302, 1257, 1221, 1169, 1116, 1028, 815, 754, 706, 456, 509 cm$^{-1}$; mp = 178−180 °C (dec); HRMS-EI ($M^+$) calcd for $C_{22}H_{20}N_2O_4$ 376.1423, found 376.1418. Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20, H, 5.36, N, 7.44. Found: C, 69.87, H, 5.29, N, 7.57.

**Synthesis of 12.** Compound **12** was prepared by a procedure analogous to the preparation of **11**, using **10** (0.1 g, 0.6 mmol) and *N*-(*tert*-butyloxycarbonyl)-1,2-diaminobenzene **4** (0.415 g, 2 mmol). Yield: 0.236 g (0.4 mmol, 72%) of **12** as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 14.05 (d, 1H, $J$ = 6.5 Hz, C═CNH), 13.67 (d, 1H, $J$ = 6.5 Hz, C═CNH), 8.87 (d, 1H, $J$ = 6 Hz, HC−N), 7.99 (d, 1H, $J$ = 6 Hz, HC−N), 7.95−7.83 (m, 2H), 7.25−7.01 (m, 4H), 6.21 (d, 1H, $J$ = 10 Hz), 1.47 (s, 18H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 181.4, 178.8, 157.8, 155.6, 154.9, 154.7, 142.1, 135.5, 135.2, 132.8, 131.9, 128.9, 127.9, 126.3, 126.0, 124.7, 123.8, 120.8, 119.7, 116.0, 111.8, 110.2, 82.6, 82.3, 29.6, 29.6 ppm; MS (EI, 70 eV) *m*/*z* 546 ($M^+$); IR $\nu$ (KBr) = 3253, 2980, 2931, 1724, 1640, 1603, 1575, 1519, 1438, 1358, 1334, 1241, 1149, 1020, 742, 493 cm$^{-1}$; mp = 183−185 °C (dec); HRMS-EI ($M^+$) calcd for $C_{30}H_{34}N_4O_6$ 546.2475, found 546.2478. Anal. Calcd for $C_{30}H_{34}N_4O_6$: C, 65.92, H, 6.27, N, 10.25. Found: C, 65.52, H, 6.42, N, 10.51.

**Synthesis of 14.** Compound **14** was prepared by a procedure analogous to the preparation of **11**, using **13** (0.1 g, 0.6 mmol) and *N*-(*tert*-butyloxycarbonyl)-1,2-diaminobenzene **4** (0.415 g, 2 mmol). Yield: 0.252 g (0.46 mmol, 77%) of **14** as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.57 (s br, 2H), 8.61 (s, 2H), 8.19 (d, 2H, $J$ = 6.5 Hz, 7.31−7.27 (m, 2H), 7.09−7.07 (m, 6H), 7.0 (s, 2H), 1.51 (s, 18H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 164.9, 153.9, 151.1, 138.9, 134.1, 129.9, 124.6, 123.4, 122.7, 120.8, 119.8, 82.4, 29.7 ppm; MS (EI, 70 eV) *m*/*z* 546 ($M^+$); IR $\nu$ (KBr) = 3443, 3382, 2976, 2923, 1728, 1611, 1587, 1543, 1479, 1438, 1390, 1362, 1306, 1229, 1145, 1108, 1044, 1020, 879, 827, 750, 617, 565 cm$^{-1}$; mp = 218−220 °C (dec). Anal. Calcd for $C_{30}H_{34}N_4O_6$: C, 65.92, H, 6.27, N, 10.25. Found: C, 65.68, H, 6.31, N, 10.44.

**Synthesis of 16.** Compound **16** was prepared by a procedure analogous to the preparation of **11**, using **15** (0.1 g, 0.6 mmol) and **4** (0.415 g, 2 mmol). Yield: 0.193 g (0.35 mmol, 69%) of **16** as an orange solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 11.79 (s br, 2H), 8.57 (s, 2H), 8.18 (d, 2H, $J$ = 6.5 Hz), 7.36−7.28 (m, 2H), 7.10−7.07 (m, 6H), 7.00 (s, 2H), 1.51 (s, 18H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 163.1, 152.8, 152.5, 137.6, 132.6, 128.6, 123.3, 122.9, 119.7, 119.5, 118.3, 81.0, 28.3 ppm; MS (EI, 70 eV) *m*/*z* 546 ($M^+$); IR $\nu$ (KBr) = 3435, 3358, 2964, 2936, 1724, 1700, 1696, 1603, 1583, 1503, 1438, 1374, 1314, 1241, 1145, 1044, 1016, 963, 883, 843, 754, 589, cm$^{-1}$; mp > 250 °C. Anal. Calcd for $C_{30}H_{34}N_4O_6$: C, 65.92, H, 6.27, N, 10.25. Found: C, 66.14, H, 6.33, N, 10.49.

**Synthesis of 18.** Compound **18** was prepared by a procedure analogous to the preparation of **11**, using **17** (0.1 g, 0.6 mmol) and **4** (0.415 g, 2 mmol). Yield: 0.256 g (0.47 mmol, 78%) of **18** as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 13.26 (s br, 2H), 8.49 (s, 2H), 8.11 (d, 2H, $J$ = 6 Hz), 7.47 (s, 1H), 7.25−7.23 (m, 2H), 7.05−7.03 (m, 4H), 6.93 (s, 2H), 6.59 (s, 1H), 1.51 (s, 18H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 165.9, 162.5, 152.6, 138.4, 137.8, 132.2, 127.8, 123.4, 119.6, 118.4, 113.6, 104.4, 80.9, 28.3 ppm; MS (EI, 70 eV) *m*/*z* 546 ($M^+$); IR $\nu$ (KBr) = 3422, 2976, 2923, 1736, 1640, 1587, 1507, 1454, 1358, 1297, 1225, 1145, 1048, 1016, 984, 871, 746, 480 cm$^{-1}$; mp = 135−137 °C (dec). Anal. Calcd for $C_{30}H_{34}N_4O_6$: C, 65.92, H, 6.27, N, 10.25. Found: C, 65.99, H, 6.20, N, 10.28.

**Synthesis of 20.** Compound **20** was prepared by a procedure analogous to the preparation of **11**, using **1** (0.137 g, 0.6 mmol) and *N*-(*tert*-butyloxycarbonyl)-1,3-diaminobenzene **19** (0.642 g, 3.1 mmol). Yield: 0.337 g (0.4 mmol, 69%) of **20** as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 13.29−13.25 and 12.97−12.89 (m, 3H), 8.70−8.63 (m, 3H), 7.46−6.90 (m, 15H), 6.67−6.61 (m, 3H), 1.26 (s, 27H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 188.9, 186.2, 186.1, 154.6, 150.1, 142.9, 141.1, 140.9, 131.9, 116.9, 113.2, 108.6, 108.3, 108.1, 107.8, 81.3, 42.2, 41.9, 41.6, 41.3, 41.1, 40.8, 40.5, 30.0 ppm; MS (EI, 70 eV) *m*/*z* 781 ($M^+$); IR $\nu$ (KBr) = 3439, 2980, 2927, 1728, 1611, 1583, 1535, 1438, 1366, 1257, 1233, 1145, 883, 750, 674, 568 cm$^{-1}$; mp = 208−210 °C (dec); HRMS-EI ($M^+$) calcd for $C_{42}H_{48}N_6O_9$ 781.3561, found 781.3549. Anal. Calcd for $C_{42}H_{48}N_6O_9$: C, 64.60, H, 6.20, N, 10.76. Found: C, 64.00, H, 6.38, N, 10.76.

**Synthesis of 21.** Compound **21** was prepared by a procedure analogous to the preparation of **11** from **10** (0.1 g, 0.6 mmol) and **19** (0.415 g, 2 mmol). Yield: 0.223 g (0.4 mmol, 68%) of **21** as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 14.10 (d, 1H, $J$ = 13 Hz), 13.56 (d, 1H, $J$ = 13 Hz), 13.28 (d, 1H, $J$ = 12 Hz), 12.75 (d, 1H, $J$ = 12 Hz), 8.91−8.82 (m, 4H), 7.76−6.89 (m, 18H), 6.03−5.99 (m, 2H), 1.46 (s, 36H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 188.3, 185.5, 161.3, 154.0, 153.9, 153.4, 153.0, 149.4, 143.4, 141.5, 141.3, 141.0, 140.7, 131.8, 131.6, 119.9, 118.9, 117.6, 116.2, 114.1, 113.6, 113.5, 112.9, 109.8, 108.3, 108.0, 82.4, 42.2, 29.7 ppm; MS (EI, 70 eV) $m/z$ 546 ($M^+$); IR $\nu$ (KBr) = 3282, 3080, 2972, 2919, 1728, 1644, 1591, 1527, 1495, 1442, 1366, 1293, 1233, 1149, 1048, 984, 867, 770, 678, 480 cm$^{-1}$; mp = 146−148 °C (dec); HRMS-EI ($M^+$) calcd for $C_{30}H_{34}N_4O_6$ 546.2478, found 546.2468. Anal. Calcd for $C_{30}H_{34}N_4O_6$: C, 65.92, H, 6.27, N, 10.25. Found: C, 65.60, H, 6.38, N, 10.34.

**Synthesis of 23.** Compound **23** was prepared by a procedure analogous to the preparation of **11**, using **1** (0.1 g, 0.5 mmol) and racemic *N*-(*tert*-butyloxycarbonyl)-*trans*-1,2-diaminocyclohexane **22** (0.336 g, 1.5 mmol). Yield: 0.283 g (0.35 mmol, 71%) of **23** as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 11.32 and 10.98−10.79 (m, 3H), 8.17−8.08 (m, 3H), 4.66−4.47 (m, 2H), 3.44 (m, 2H), 2.96−2.92 (m, 2H), 2.26−2.01 (m, 6H), 1.76−1.70 (m), 1.47−1.29 (m), 1.11−1.02 (m) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 187.4, 185.0, 182.8, 156.7, 155.9, 155.2, 104.5, 104.4, 79.4, 64.8, 63.8, 53.6, 32.3, 32.2, 32.0, 28.3, 28.2, 28.1, 24.8, 24.3 ppm; ESI-MS $m/z$ = 799 (M + $H^+$); IR $\nu$ (KBr) = 3406, 3278, 2927, 2859, 2384, 2344, 2332, 1716, 1700, 1676, 1595, 1555, 1503, 1454, 1382, 1313, 1157, 1092, 1000, 959, 839, 694, 609, 569, 517 cm$^{-1}$; mp = 94−95 °C. Anal. Calcd for $C_{42}H_{66}N_6O_9$: C, 63.13, H, 8.33, N, 10.52. Found: C, 62.74, H, 8.15, N, 10.66.

**Synthesis of 24.** Compound **24** was prepared by a procedure analogous to the preparation of **11**, using **10** (0.1 g, 0.6 mmol) and **22** (0.171 g, 1.2 mmol). Yield: 0.214 g (0.38 mmol, 64%) of **24** as a light yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.40 (s), 11.68 (s), 11.48 (s), 10.92−10.86 (m), 8.39−8.33 (m), 7.23−7.11 (m), 6.78−6.74 (m), 5.80−5.52 (m), 5.06−4.65 (m), 3.43−3.08 (m), 1.99−195 (m), 1.72−1.70 (m), 1.50−1.41 (m), 1.37−1.17 (m), 0.82−0.76 (m) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 186.0, 185.4, 185.3, 183.1, 159.1, 158.2, 156.0, 155.2, 141.6, 141.1, 115.9, 115.8, 115.1, 109.3, 109.2, 104.5, 104.3, 79.5, 64.4, 62.8, 53.8, 32.7, 32.3, 32.2, 31.8, 28.9, 28.3, 28.1, 28.1, 28.1, 28.0, 24.5, 24.3 ppm; MS (EI, 70 eV) $m/z$ 558 ($M^+$); IR $\nu$ (KBr) = 3443, 3334, 2984, 2936, 2859, 1712, 1652, 1607, 1535, 1378, 1358, 1302, 1233, 1157, 1012, 996, 847, 766, 698, 629, 521 cm$^{-1}$; mp = 163−165 °C (dec). Anal. Calcd for $C_{30}H_{46}N_4O_6$: C, 64.49, H, 8.30, N, 10.03. Found: C, 64.29, H, 8.15, N, 9.87.

**Synthesis of 25.** Under a nitrogen atmosphere di-*tert*-butyl dicarbonate (3.0 g, 13.7 mmol) was added to a mixture of 1,8-diaminonaphthalene (2 g, 12.6 mmol) and triethylamine (2 mL, 14 mmol) in 50 mL of dry THF. The mixture was stirred for 12 h at room temperature and the solvent removed under reduced pressure. The obtained off-white solid was dissolved in 30 mL of toluene and washed with NaOH (1 N, 10 mL), brine (10 mL) and $H_2O$ (10 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed by rotary evaporation. Recrystallization from hexanes afforded **25** as red crystals (2.6 g, 10.2 mmol, 81%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.69 (br s, 1H), 8.03 (d, 1H, $J$ = 6 Hz), 7.47−7.17 (m, 4H), 6.78 (d, 1H, $J$ = 5.5 Hz), 4.02 (s br, 2H), 1.49 (s, 9H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 153.1, 140.7, 136.2, 135.3, 126.0 125.4, 123.5, 122.6, 119.3, 118.8, 116.8, 116.7, 80.0, 28.4 ppm; MS (EI, 70 eV) $m/z$ 258 ($M^+$); IR $\nu$ (KBr) = 3378, 3298, 3205, 3048, 2984, 2923, 2879, 1925, 1708, 1696, 1603, 1539, 1499, 1430, 1346, 1237, 1153, 1076, 976, 887, 819, 754, 658, 625, 468 cm$^{-1}$; mp = 89−90 °C. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74, H, 7.02, N, 10.84. Found: C, 70.07, H, 7.20, N, 10.90.

**Synthesis of 26.** Compound **26** was prepared by a procedure analogous to the preparation of **11**, by reaction of **10** (0.05 g, 0.3 mmol) with **25** (0.155 g, 0.6 mmol) in ethanol. Yield: 0.120 g (0.19 mmol, 62%) of **26** as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 11.76 (s, 1H), 10.80 (s, 1H), 9.00 (s, 1H), 8.98 (d, 2H, $J$ = 8 Hz), 8.05 (d, 1H, $J$ = 6 Hz), 7.72 (d, 1H, $J$ = 6 Hz), 7.66 (d, 1H, $J$ = 6 Hz), 7.54−7.32 (m, 7H), 7.03−6.97 (m, 2H), 6.95 (d, 1H, $J$ = 3 Hz), 6.83 (d, 1H, $J$ = 5 Hz), 6.21 (d, 1H, 6.5 Hz), 4.93 (d, 1H, $J$ = 3 Hz); 1.54 (s, 9H), 1.12 (s, 9H) ppm; $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 161.4, 161.3, 159.6, 157.8, 153.0, 147.7, 135.8, 135.1, 135.0, 133.8, 132.6, 130.9, 128.3, 127.9, 127.5, 126.7, 126.6, 126.4, 126.4, 126.0, 125.5, 123.8, 123.7, 123.4, 123.1, 119.4, 119.4, 117.7, 117.4, 117.3, 109.9, 108.9, 107.6, 83.2, 79.9, 79.8, 79.5, 63.1, 53.3, 28.2, 27.8 ppm; ESI-MS $m/z$ = 647 (M+$H^+$); IR $\nu$ (KBr) = 3410, 3358, 3060, 2968, 2923, 1688, 1607, 1563, 1523, 1487, 1426, 1354, 1318, 1229, 1145, 1072, 1040, 980, 815, 758, 529, 456 cm$^{-1}$; mp = 146−148 °C (dec). Anal. Calcd for $C_{38}H_{38}N_4O_6$: C, 70.57, H, 5.92, N, 8.66. Found: C, 70.77, H, 6.10, N, 9.06.

**Computations**. Ab initio DFT calculations were performed using Spartan '04 for Windows (Wavefunction Inc., Irvine, CA). Both the keto and enol isomers of **27**−**33** were geometry minimized using the B3LYP method with a 6-31G* basis set. For each molecule, the calculation was started with different possible orientations of the peripheral benzene rings until the minimum energies (which we are confident are at least very close to the global minimum) were determined, then a B3LYP/6-31G** single point calculation was performed. In the cases of **27** and **32**, geometry minimized structures with B3LYP/6-31G** were almost identical with respect to bond lengths and bond angles to those determined by B3LYP/6-31G*. The energies of the B3LYP/6-31G* structures are tabulated in Tables 1 and 2. AM1 and PM3 geometry optimization calculations were performed beginning with the geometries obtained from B3LYP/6-31G*.

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**Supporting Information Available:** X-ray crystallographic data for **12** and **26** (CIF format); general experimental methods; synthesis of **7**, **8**, and **19**; NMR spectra of all new compounds; VT NMR data; and atomic coordinates for calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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