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Ene-diamine versus Imine-amine Isomeric Preferences

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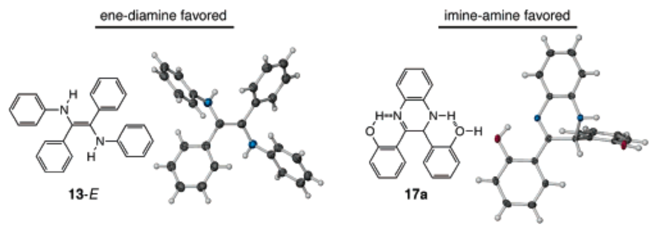
Received June 1, 2005

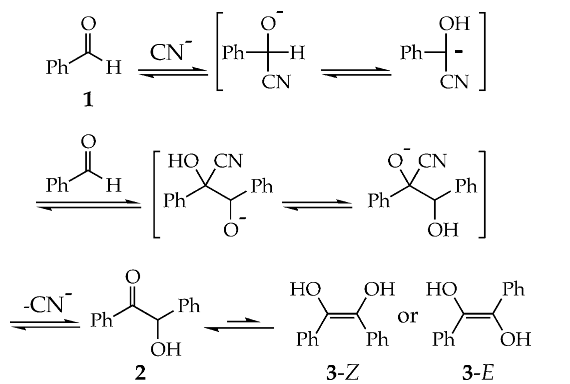


Cyanide-catalyzed aldimine coupling was employed to synthesize compounds with 1,2-ene-diamine and α-imine-amine structural motifs: 1,2,*N*,*N*′-tetraphenyletheylene-1,2-diamine (**13**) and (±)-2,3-di-(2-hydroxyphenyl)-1,2-dihydroquinoxaline (**17**), respectively. Single-crystal X-ray diffraction provided solid-state structures and density functional theory calculations were used to probe isomeric preferences within this and the related hydroxy-ketone/ene-diol system. The ene-diamine and imine-amine core structures were calculated (B3LYP/6-311++G(d,p)) to be essentially identical in energy ($\Delta G = 0.2$ kcal/mol in favor of the imine-amine, within the error of the calculation). However, additional effects—such as π conjugation—in **13** render an ene-diamine structure that is slightly more stable than the imine-amine tautomer (**14**) ($\Delta G = 0.2-0.7$ kcal/mol, within the error of the calculation). In contrast, the intramolecular hydrogen bonding present in **17** significantly favors the imine-amine isomer over the ene-diamine tautomer (**18**) ($\Delta G = 7.2-8.9$ kcal/mol). For both **13** and **17**, the optimized calculated structures (B3LYP/6-31+G(d′)) are identical to those observed by single-crystal X-ray diffraction.

Introduction

Hydroxy-ketone vs Ene-diol Isomers. The cyanide-catalyzed benzoin condensation reaction was apparently first reported by Stange in 1824.[1,2] The commonly accepted mechanism, generally attributed to Lapworth,[3] produces the stable α-Hydroxy-ketone (**2**, benzoin), but avoids the intermediacy of a 1,2-ene-diol structure such as **3**-*Z* or **3**-*E* (Scheme 1).[4]

SCHEME 1. The 1,2-Ene-diol Isomers 3-*Z* and 3-*E* Are Not Observed in the Benzoin Condensation Reaction

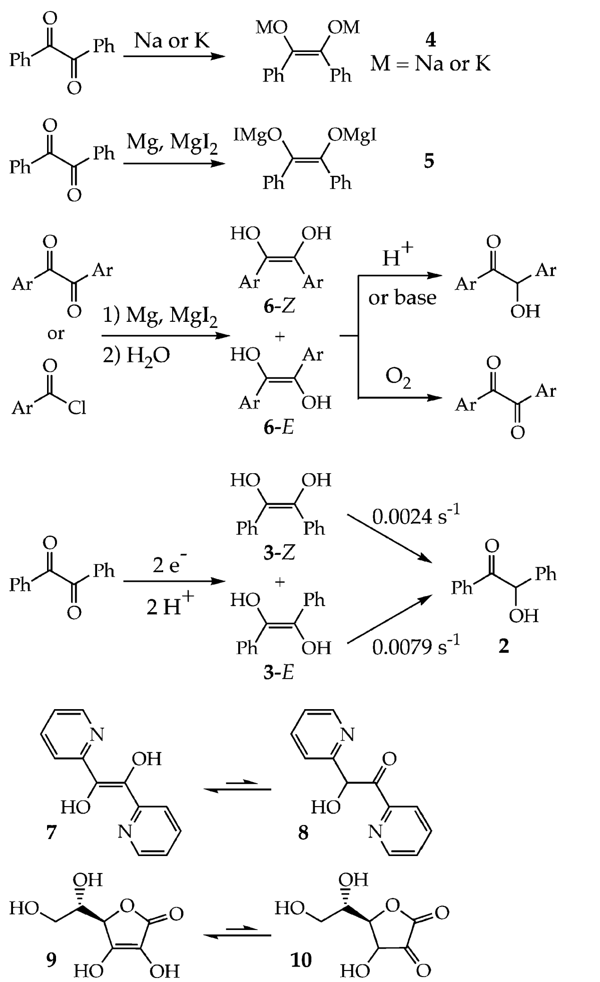


Ene-diol structures akin to **3**-*Z* and **3**-*E* have garnered considerable interest over the past century in synthetic, analytical, and theoretical chemistry (Scheme 2). Ene-diolates such as **4**-Na, **4**-K, and **5** are stable and can be prepared by reduction,[5−7] but the ene-diol **6** is only stable under neutral, anaerobic conditions when the aryl group

(1) Stange, C. *Repertorium für die Pharmacie* **1824**, *16*, 80−107.
(2) The benzoin condensation is technically a dimerization since the molecular weight of benzoin is twice that of benzaldehyde. Hence, the term "coupling" is used here to avoid the misleading descriptor "condensation" and is meant to apply generally to intermolecular and intramolecular reactions.
(3) (a) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995−1005. (b) Lapworth, A. *J. Chem. Soc.* **1904**, *85*, 1206−1213.
(4) Kuebrich, J. P.; Schowen, R. L.; Wang, M.; Lupes, M. E. *J. Am. Chem. Soc.* **1971**, *93*, 1214−1220.
(5) Nef, J. V. *Justus Liebigs Ann. Chem.* **1899**, *308*, 264−334.
(6) Staudinger, H.; Binkert, A. *Helv. Chim. Acta* **1922**, *17*, 703−710.

10.1021/jo051102g CCC: $30.25
Published on Web 09/09/2005

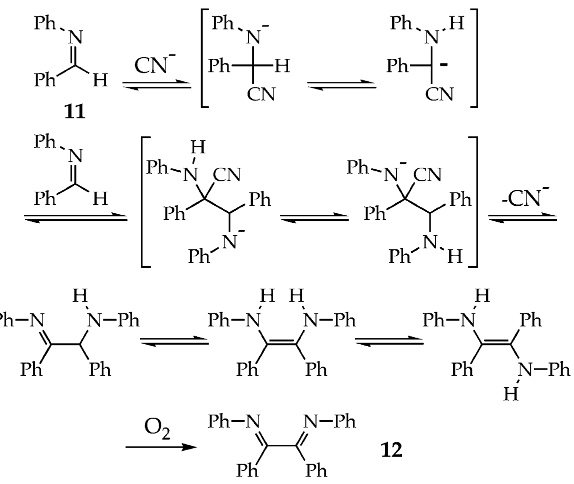
SCHEME 2. Stable (4, 5, 7, 9) and Metastable (3, 6) Molecules Bearing the Ene-diolate or Ene-diol Motif



is highly substituted (Ar = 2,4,6-trimethylphenyl, 2,4,6-triethylphenyl, or 2,6-diethylphenyl).[8,9] The electrochemical reduction of benzil leads to ephemeral ene-diols.[10,11] It was shown that **3**-*E* tautomerizes to benzoin somewhat faster than does **3**-*Z*.[12] The 1,2-ene-diol motif is known to exist in a stable form in a limited number of molecules. For example, *trans*-1,2-di-(2-pyridyl)-ethylene-1,2-diol (**7**, α-pyridoin)[13] and L-ascorbic acid (**9**, vitamin C)[14] both exist as ene-diols. Notably, **7** and **9** are stabilized by intramolecular hydrogen bonding in the solid state.

While several accounts describe the kinetic details of interconversion among hydroxy-ketone/ene-diol

SCHEME 3. Intermolecular Aldimine Coupling: Dimerization



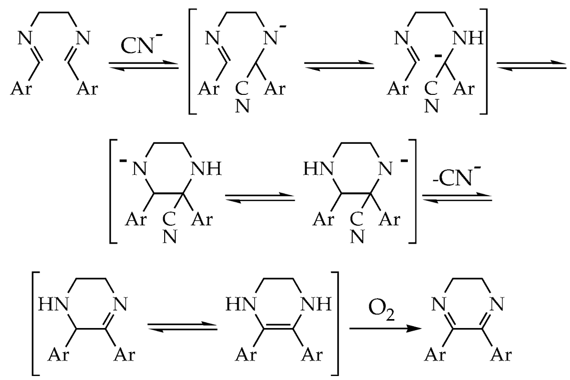
isomers,[10−12,15] thermodynamic details are relatively sparse. The experimentally determined equilibrium constant between *E*-stilbenediol (**3**-*E*) and *Z*-stilbenediol (**3**-*Z*)—measured via electrochemical reduction of benzil—was found to favor the *E* isomer by 1.7 kcal/mol at pH 7.[16] Additionally, quantum chemical calculations suggest that benzoin (**2**) is 7.6 kcal/mol lower in energy than *Z*-stilbenediol (**3**-*Z*).[17] This result implies that the hydroxy-ketone core structure has significantly stronger inherent bonding than the ene-diol core structure.

Ene-diamine vs Imine-amine Isomers. The cyanide-catalyzed aldimine coupling reaction (AIC) is analogous to the benzoin reaction and likely proceeds through a similar mechanism.[18,19] The proposed mechanism for *intermolecular* AIC involves cyanide attack at an aldimine and tautomerization to form a carbanion; this nucleophile attacks a second aldimine and the subsequent tautomerization is followed by elimination of cyanide (Scheme 3). The proposed mechanism for *intramolecular* AIC cyclization is similar except that the nucleophilic attack proceeds intramolecularly (Scheme 4).[20] Aerobic conditions for either reaction generally afford α-diimines, but anaerobic or phase-transfer conditions can prevent the final oxidation step, in which case an ene-diamine or imine-amine should result.

Despite the number of accounts describing isomerism in the hydroxy-ketone/ene-diol system, relatively little has been reported for the ene-diamine/imine-amine system. Strain recognized the existence of multiple isomers for dimerized *N*-benzylideneaniline in an early manuscript,[21] but did not recognize all possible isomers. For the prototypical dimerization of *N*-benzylideneaniline (**11**), the product could exist as six possible isomers:

(7) Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1927**, *49*, 2584−2592.
(8) (a) Fuson, R. C.; Corse, J. *J. Am. Chem. Soc.* **1939**, *61*, 975. (b) Fuson, R. C.; Corse, J.; McKeever, C. H. *J. Am. Chem. Soc.* **1939**, *61*, 2010−2012. (c) Fuson, R. C.; Scott, S. L.; Horning, E. C.; McKeever, C. H. *J. Am. Chem. Soc.* **1940**, *62*, 2091−2094.
(9) Thompson, R. B. *J. Am. Chem. Soc.* **1939**, *61*, 1281−1283.
(10) (a) Pasternak, R. *Helv. Chim. Acta* **1947**, *30*, 1984−1999. (b) Pasternak, R. *Helv. Chim. Acta* **1948**, *31*, 753−776.
(11) Vincenz-Chodkowska, A.; Grabowski, Z. R. *Electrochim. Acta* **1964**, *9*, 789−801.
(12) (a) Stapelfeldt, H. E.; Perone, S. P. *Anal. Chem.* **1968**, *40*, 815−818. (b) Stapelfeldt, H. E.; Perone, S. P. *Anal. Chem.* **1969**, *41*, 623−627.
(13) Ashida, T.; Hirokawa, S.; Okaya, Y. *Acta Crystallogr.* **1965**, *18*, 122−127.
(14) (a) Hvoslef, J. *Acta Crystallogr.* **1968**, *B24*, 23−35. (b) Hvoslef, J. *Acta Crystallogr.* **1968**, *B24*, 1431−1440.
(15) (a) Dominguez, M.; Roldan, E.; Carbajo, J.; Calvente, J.; Gonzalez-Arjona, D.; Andreu, R. *J. Electroanal. Chem.* **1991**, *316*, 133−142. (b) Johnson, D. C.; Gaines, P. R. *Anal. Chem.* **1973**, *45*, 1670−1675.
(16) Meunier-Prest, R.; Laviron, E.; Gaspard, C.; Raveau, S. *Electrochim. Acta* **2001**, *46*, 1847−1861.
(17) Pawelka, Z.; Kryachko, E. S.; Zeegers-Huyskens, T. *Chem. Phys.* **2003**, *287*, 143−153.
(18) Strain, H. H. *J. Am. Chem. Soc.* **1928**, *50*, 2218−2223.
(19) Correia, J. *J. Org. Chem.* **1983**, *48*, 3343−3344.
(20) Reich, B. J. E.; Justice, A. K.; Beckstead, B. T.; Reibenspies, J. H.; Miller, S. A. *J. Org. Chem.* **2004**, *69*, 1357−1359.
(21) Strain, H. H. *J. Am. Chem. Soc.* **1929**, *51*, 269−273.

SCHEME 4. Intramolecular Aldimine Coupling: Cyclization



E-1,2,*N*,*N*′-tetraphenylethylene-1,2-diamine (**13**-*E*); *Z*-1,2,-*N*,*N*′-tetraphenylethylene-1,2-diamine (**13**-*Z*); (*S*)-*E*-phenyl-(2-phenylimino-1,2-diphenylethyl)-amine (**14**-*S*-*E*); (*R*)-*E*-phenyl-(2-phenylimino-1,2-diphenylethyl)-amine (**14**-*R*-*E*); (*R*)-*Z*-phenyl-(2-phenylimino-1,2-diphenylethyl)-amine (**14**-*R*-*Z*); and (*S*)-*Z*-phenyl-(2-phenylimino-1,2-diphenylethyl)-amine (**14**-*S*-*Z*) (Figure 1).

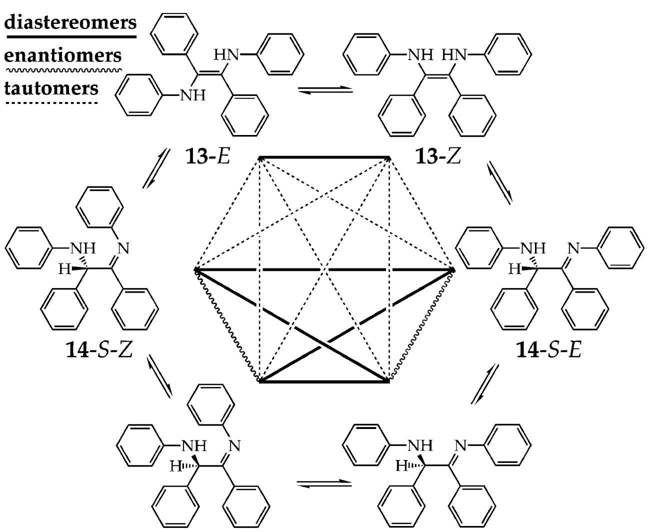
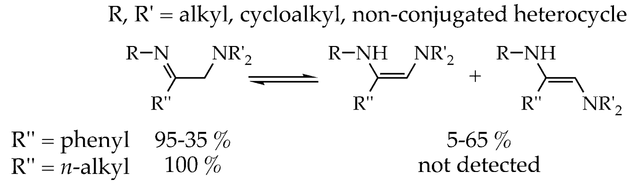


FIGURE 1. Six possible isomeric products of the cyanide-catalyzed aldimine coupling of *N*-benzylideneaniline (**11**).

Among the existing reports, there is disagreement over the preferred isomeric form of the *N*-benzylideneaniline dimer, which has not been conclusively established. Strain originally invoked an imine-amine isomer (**14**) because hydrolysis afforded the α-hydroxy-imine.[21] Later, Becker cited NMR evidence for the prevalence of an imine-amine isomer (**14**),[22] but subsequently suggested that an extensively conjugated 1,2-ene-diamine (**13**-*E* **or 13**-*Z*) is more consistent with UV−visible absorption spectra.[23] Cariou also suggested this structural assignment, but only fully *N*-alkylated products, bearing no acidic hydrogens, were characterized.[24]

The sole experimental investigation that elaborated on the isomerization between ene-diamines and imine-amines involved the ^{1}H NMR spectra of a series of

SCHEME 5. Population Distributions at 35 °C in $CDCl_3$ for Imine-amines and Ene-diamines[25]



aromatic imine-amines and aliphatic imine-amines at 35 °C in $CDCl_3$ (Scheme 5).[25] In the aromatic cases (R″ = Ph), both tautomeric forms were observed. However in the aliphatic cases (R″ = *n*-alkyl), the ene-diamine tautomer was not detected.

In the hydroxy-ketone/ene-diol system, there seems to be a strong preference to populate the hydroxy-ketone tautomer. However, there is no consistent tautomeric preference in the ene-diamine/imine-amine system; these structures are apparently similar in energy. Our continued investigation of the cyanide-catalyzed aldimine coupling reaction has revealed new synthetic routes to ene-diamine/imine-amine structures, allowing characterization of such compounds with unprecedented detail. Herein, we seek to combine this newfound experimental accessibility with theoretical calculations to disentangle the bonding energetics that are responsible for the aforementioned isomeric and tautomeric preferences.

Results and Discussion

X-ray Crystallography. To resolve structural claims and to examine the relevant isomeric preferences, we have structurally characterized two exemplary products of aldimine coupling by single-crystal X-ray diffraction. The solid-state structures of the products arising from the dimerization of *N*-benzylideneaniline (**11**) and the cyclization of salophen (**16**)[20] have been elucidated (Scheme 6). Straightforward examination of the geometry and substitution at carbon reveals that ene-diamine **13**-*E* is the preferred form of the *N*-benzylideneaniline dimer, while cyclized salophen exists as the imine-amine isomer **17a**. Note that the latter is stabilized by intramolecular hydrogen bonding.

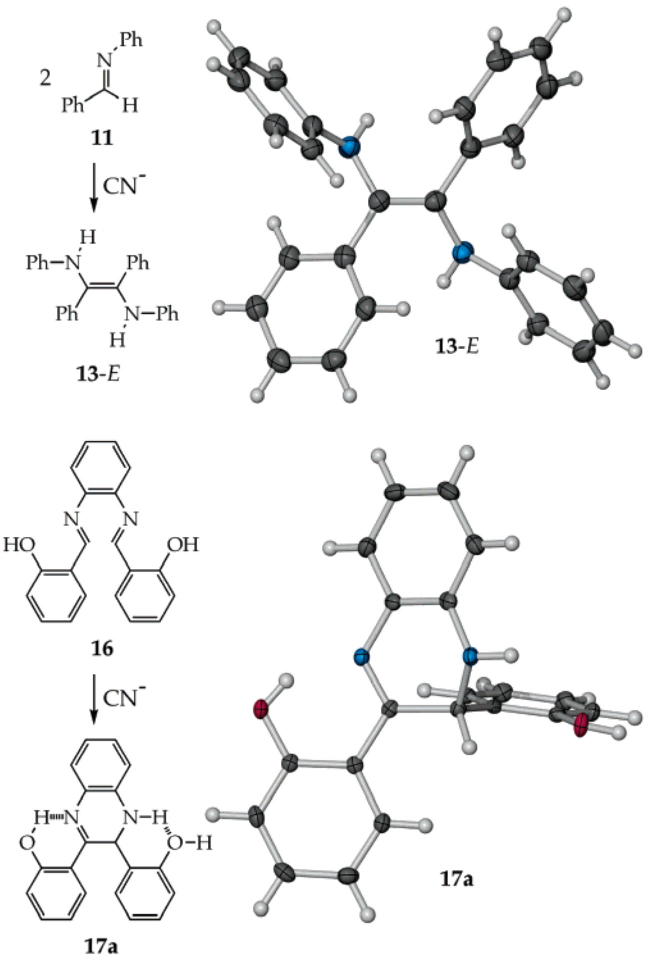
NMR Investigations. ^{1}H NMR and ^{13}C NMR room-temperature solution spectra of cyclized salophen (**17a**) are essentially consistent with the C_1-symmetric solid-state structure. Twenty distinct carbon peaks exist as well as four distinct nonaromatic proton peaks, corresponding to the hydrogens on the lone sp^3 carbon, the amine nitrogen, and the two different oxygens. In contrast, the ^{1}H NMR spectrum of *E*-1,2,*N*,*N*′-tetraphenylethylene-1,2-diamine (**13**-*E*) consists of broad peaks with several resonances unaccounted for by the solid-state structure. This finding suggests the possibility of multiple equilibrating isomers in solution.

To address the question of equilibrating isomers, crystals of **13**-*E* were dissolved in $CDCl_3$ and multiple

(22) Becker, H.-D. *J. Org. Chem.* **1964**, *29*, 2891−2894.
(23) Becker, H.-D. *J. Org. Chem.* **1970**, *35*, 2099−2102.

(24) Several compounds of the type PhMeN(Ar)C=C(Ar)NMePh were synthesized, separated by column chromatography, and assigned as *E* or *Z* based on λ_{max} in the UV−visible spectrum, NMR evidence, and melting points. Cariou, M.; Carlier, R.; Simonet, J. *Bull. Soc. Chim. Fr.* **1986**, *5,* 781−792.
(25) Duhamel, P.; Duhamel, L.; Legal, J.-C. *C. R. Acad. Sci. Ser. C: Sci. Chim.* **1970**, *271*, 156−158.

SCHEME 6. Dimerization of 11 Affords the Ene-diamine 13-*E*, whereas the Cyclization of 16 Yields the Imine-amine 17a[a]



[a] X-ray structures are depicted with 50% ellipsoids.

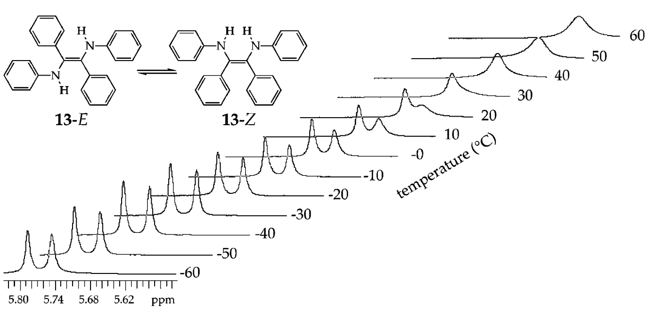


FIGURE 2. Variable temperature ^{1}H NMR spectra of the N−H region from −60 to 60 °C of dimerized *N*-benzylideneaniline **13** in $CDCl_3$.

^{1}H NMR and ^{13}C NMR spectra were taken between −60 and 60 °C. The ^{1}H NMR spectra depict amine proton peaks that coalesce at high temperature, but are fully resolved with approximately equal intensity at −25 °C (Figure 2). The resolved peaks (5.79 and 5.75 ppm) are attributed to the static structures of **13**-*E* and **13**-*Z*. The ^{13}C NMR data corroborate this assignment, as there are 18 peaks in the ^{13}C NMR spectrum at low temperatures, corresponding to 9 peaks arising from **13**-*E* and 9 peaks arising from **13**-*Z*. The presence of imine-amine isomers

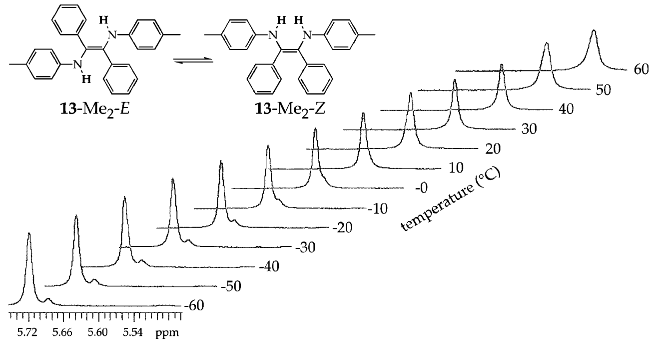


FIGURE 3. Variable temperature ^{1}H NMR spectra of the N−H region from −60 to 60 °C of dimerized *N*-benzylidenetoluidine (**13**-Me$_2$) in $CDCl_3$.

(**14**) is discounted because each should introduce 18 new peaks; these are not observed.

We can estimate the rate of exchange at the coalescence temperature (ca. 50 °C) as $k = 27\ s^{-1}$, which corresponds to a $\Delta G^{\ddagger}_{(50°C)}$ for *E* to *Z* isomerization of 16.8 kcal/mol (based on a 12.3 Hz peak separation at −60 °C).[26] This is much lower than the 41−46 kcal/mol energy barrier for *E*/*Z* isomerization in stilbene,[27] presumably because of the energetically accessible imine-amine intermediate **14**. To further validate our claims, we have synthesized the dimer of *N*-benzylidenetoluidine (**13**-Me$_2$) and see similar effects for the amine (Figure 3) and methyl protons, as well as an increase in the number of ^{13}C NMR peaks at low temperature (a 2-fold increase is not fully realized using a 300 MHz instrument because the ^{13}C NMR peaks are in a 9:1 *E*:*Z* ratio and the smaller ones are not all clearly apparent).

After demonstrating equilibration among dimerized *N*-benzylideneaniline isomers, we investigated a similar phenomenon in cyclized salophen (**17**). Because of hydrogen bonding available to **17**, we anticipated the imine-amine to be favored. We also expected that—at least at high temperatures—tautomerization would allow the facile exchange of the hydrogen bond between the two N/O pairs in the molecule, resulting in a time-averaged species with an apparent increase in symmetry. However, upon heating to 130 °C, the ^{1}H NMR spectrum of **17** (in $Cl_2DCCDCl_2$) showed flattening of the already broad amine peak, but no other peaks changed significantly. Also, the number of peaks in the ^{13}C NMR spectrum did not halve at high temperatures, further suggesting there is not rapid equilibration between the two degenerate imine-amines at 130 °C (Figure 4). This observation implies the persistence of C_1-symmetry, a relatively high barrier to tautomerization, and unusually strong hydrogen bonding in **17**. This additional bonding, not available in **13**, readily explains the energetic preference of the imine-amine tautomer over the ene-diamine tautomer.

Energetics. According to average bond dissociation energies obtained from a standard physical organic chemistry textbook, the generally prevailing hydroxy-

(26) Kegley, S. E.; Pinhas, A. R. *Problems and Solutions in Organometallic Chemistry*; University Science Books: Mill Valley, CA, 1986; pp 20−26.

(27) (a) Santoro, A. V.; Barrett, E. J.; Hoyer, H. W. *J. Am. Chem. Soc.* **1967**, *89*, 4545−4546. (b) Meier, H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1399−1420. (c) Han, W.-G.; Lovell, T.; Liu, T.; Noodleman, L. *Chemphyschem* **2002**, *3*, 167−178.

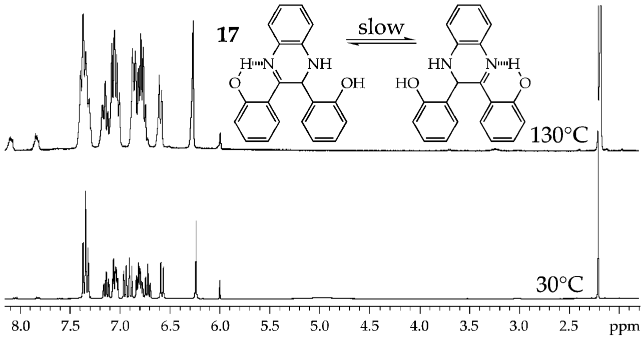


FIGURE 4. Variable temperature ^{1}H NMR of cyclized salophen (**17**) in $Cl_2DCCDCl_2$ at 30 °C and 130 °C.

ketone structure is 11 kcal/mol more stable than the ene-diol structure.[28] Similar calculations predict that the imine-amine motif is more stable than the ene-diamine motif by 19 kcal/mol. This latter calculation is contrary to the solid-state structure of dimerized *N*-benzylidene-aniline, which exists as the *E*-ene-diamine isomer **13**-*E*, but is congruent with the solid-state structure of cyclized salophen, which exists as the imine-amine isomer **17**. Because simple average bond dissociation energies cannot explain the observed isomeric preferences, quantum chemical calculations were pursued.

DFT Calculations. Geometry optimizations and frequency calculations for **2**, **3**, **13**, **14**, **17**, and **18** were performed using B3LYP/6-31+G(d′) with pure d orbitals and all energies include zero-point energy.[29]

Among the benzoin isomers **2**, **3**-*Z*, and **3**-*E* (Figure 5), the hydroxy-ketone **2** is predicted by average bond dissociation energies, NMR evidence, and the solid-state structure to be the most stable isomer.[30] A calculated energy difference of 12.1 kcal/mol between **2** and **3**-*Z* is larger than the 7.6 kcal/mol (B3LYP/6-31+G(d,p)) reported by Pawelka et al.[17] A calculated energy difference of 2.6 kcal/mol in favor of **3**-*Z* over **3**-*E* is contradicted by Benson additivities[31]—which generally favor *E*-alkenes by 1.1 kcal/mol—and is also contradicted by cyclic voltammetry experiments,[16] which showed **3**-*Z* to be higher in energy than **3**-*E* by 1.7 kcal/mol in aqueous solution. We suspect that the energetic discrepancy is largely related to intramolecular hydrogen-bonding stabilization of **3**-*Z* in the gas phase, which becomes less important in aqueous solution when intermolecular hydrogen bonding is prevalent.

DFT calculations were performed for isomers of **13**-*E*, **13**-*Z*, **14**-*E*, **14**-*Z*, **17a**, **17b**, **18a**, **18b**, and **18c** (Figure 6). Among compounds **13**−**14**, the *E*-ene-diamine **13**-*E* is the most stable.[32] Among compounds **17**−**18**, the imine-amine **17a** is the most stable. These theoretical results are in agreement with the aforementioned single-crystal X-ray diffraction studies. For compounds **13**−**14**, three different isomers are calculated to be within 0.7 kcal/mol of one another. The difference between the two most stable isomers in **17**−**18** (**17a** and **17b**) is 1.7 kcal/mol, and the difference between the least favorable isomer **18c** and the most favorable isomer **17a** is 15.9 kcal/mol, which is the largest energy difference seen among the presented models.

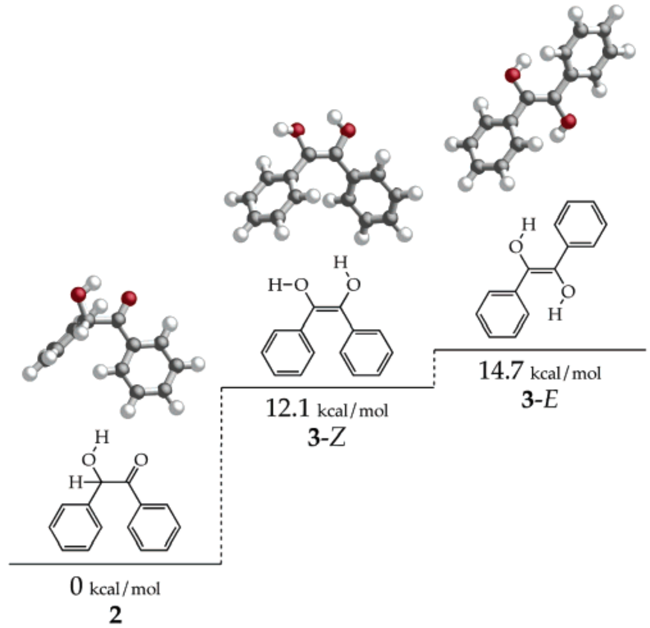


FIGURE 5. DFT optimized structures and relative gas-phase Gibbs free energies (298.15 K) of benzoin isomers **2**, **3**-*Z*, and **3**-*E*.

DFT Small Model Calculations. Geometry optimizations and frequency calculations for **19**, **20**, **21**, and **22** were performed using B3LYP/6-311++G(d,p) with pure d orbitals and all energies include zero-point energy.

DFT calculations were performed on several isomers and rotamers of ethylene-1,2-diamine, a model substrate with reduced size for computational tractability (Figure 7). The *Z*-ene-diamine (**19**-*Z*) is the most stable isomer, with an energy of 2.2 kcal/mol below that of the next closest isomer **20a**-*E*. The stabilizing energy of the intramolecular hydrogen bond in **20a**-*E* can be estimated by taking the energy difference between **20a**-*E* and **20b**-*E*, which is 1.0 kcal/mol. The stabilizing energy of the intramolecular hydrogen bonding in **19**-Z is difficult to estimate because each rotamer has a hydrogen bond or a lone pair/lone pair interaction. Neither imine-amine **20b**-*E* nor ene-diamine **19**-*E* is stabilized by intramolecular hydrogen bonding. Hence, the *inherent* energetic difference between these two tautomeric structures is approximately 0.2 kcal/mol, with a slight preference for the imine-amine.[32] This sharply contrasts with the energetic difference between the corresponding oxygen analogues, *s-trans*-hydroxy-acetaldehyde (**21**) and *E*-eth-

(28) Values from: Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry,* 3rd ed.; HarperCollinsPublishers: New York, 1987; pp 161−162. See the Supporting Information.

(29) The present electronic structure calculations are limited to the gas phase and detailed solvent models are beyond the scope of this paper. The calculations would likely be improved by employing continuum solvent models (like polarizable continuum (PCM) or conductor-like-screening (COSMOS)), although these consider general solvent molecules and would not capture specific hydrogen bonding with a particular type of solvent. Correcting the calculated gas-phase entropies for solvent effects may also offer some improvement on the present calculated Gibbs free energies. However, such corrections would not likely offer insight that greatly affects the present conclusions and these effects have, therefore, been neglected.

(30) Haisa, M.; Kashino, S.; Morimoto, M. *Acta Crystallogr.* **1980**, *B36*, 2832−2834.

(31) Cohen, N.; Benson, S. W. *Chem. Rev.* **1993**, *93*, 2419−2438.

(32) Note that the uncertainty of these theoretical calculations is 1−3 kcal/mol. Accordingly, the energetic ordering of structures within this range cannot be made with unqualified certitude.

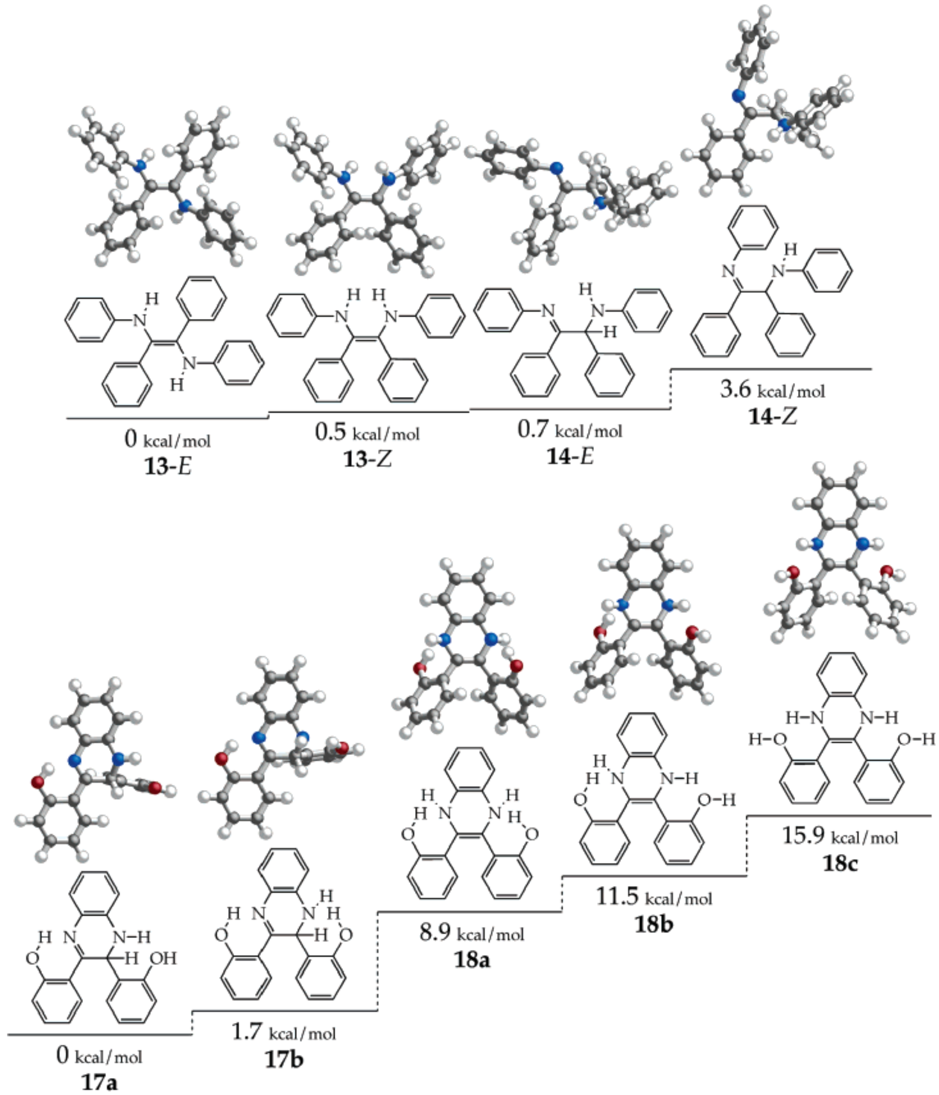


FIGURE 6. DFT optimized structures and relative gas-phase Gibbs free energies (298.15 K) for various isomers **13**−**14** and **17**−**18**.

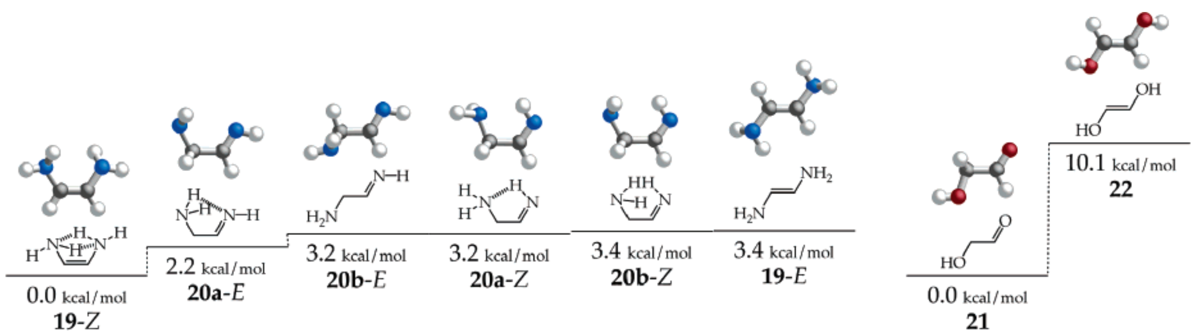


FIGURE 7. DFT optimized structures and relative gas-phase Gibbs free energies (298.15 K) for **19**−**20**, **21**, and **22**.

ylene-1,2-diol (**22**); the hydroxy-aldehyde structure (cf. benzoin) is calculated to be more stable than the enediol structure by 10.1 kcal/mol (Figure 7).

These computational results are in approximate agreement with quantum chemical calculations by Lien and Chuang carried out at three different levels of theory.[33] Their calculations indicate that *E*-ethylene-1,2-diamine (**19**-*E*) is 4.33 (HF/6-31G**), 1.96 (B3LYP/6-31G**), or 2.15 (G2) kcal/mol higher in energy than 2-imino-ethylamine (**20b**-*E*). Our calculated value of 0.2 kcal/mol for the **19**-*E*/**20b**-*E* energetic difference involves a considerably larger basis set (triple-ζ split-valence polarized basis set with additional diffuse functions as opposed to a double-ζ split-valence polarized basis set) than the cor-

(33) Chuang, C.-H.; Lien, M.-H. *Eur. J. Org. Chem.* **2004**, *2004*, 1432−1443.

responding B3LYP calculation that yielded 1.96 kcal/mol. The increased basis set size generally provides a more accurate result, presuming the methodology offers a reasonable description of the electronic structure.[34–36] Also indicated by Lien and Chuang is that **22** is 14.27 (HF/6-31G**), 9.75 (B3LYP/6-31G**), or 10.23 (G2) kcal/mol higher in energy than **21**. These latter two determinations are in accord with our calculated value of 10.1 kcal/mol.

Despite the fact that the computationally investigated nitrogen-containing compounds (**13**–**14**, **17**–**18**, **19**–**20**) preferred three different lowest energy isomers, a unifying theme appeared: *unlike analogous products of the benzoin condensation, the E-ene-diamine, Z-ene-diamine, and imine-amine core structures are energetically similar*. In the hydroxy-ketone/ene-diol system, the difference in energy between the two core structures is large, and interactions such as steric hindrance, π electron effects (conjugation), or hydrogen bonding do little to change isomeric preference. *In the ene-diamine/imine-amine system, core structure energy differences are small and thus, steric hindrance, π electron effects, and hydrogen bonding are the determining factors for isomeric preference.*

Conclusions

Energetically, the hydroxy-ketone/ene-diol system is quite different from the structurally analogous ene-diamine/imine-amine system. Theoretical investigations into isomeric preferences for products of the benzoin condensation show that the hydroxy-ketone motif is favored by 10–15 kcal/mol over the ene-diol tautomers. In contrast, experimental and theoretical investigations into isomeric preferences for products of aldimine coupling show that the three core structures (*E*-ene-diamine, *Z*-ene-diamine, and imine-amine) have similar energetics (range = 3 kcal/mol); quantum chemical calculations suggest that isomeric preference is determined by factors other than inherent bonding such as steric hindrance, π electron effects, and hydrogen bonding. Among these, hydrogen bonding is most important (see **17a**) and structures that lack hydrogen bonding are likely to assume the isomer that best minimizes steric interactions and maximizes conjugation (see **13**-*E*). The single-crystal X-ray structures of **13**-*E* and **17a** match those optimized at the B3LYP/6-31+G(d′) level, suggesting that this level of theory is appropriate and suitable for investigating ene-diamine and imine-amine isomeric preferences.

Experimental Section

Theoretical Methods. All calculations were performed using the Gaussian 03[37] suite of programs. Optimized structure and frequency calculations were performed using density functional theory (DFT) employing the Becke's three-parameter hybrid functional (B3)[38] with the correlation functional of Lee, Yang, and Parr (LYP),[39,40] and the Pople style basis sets, 6-31+G(d′) and 6-311++G(d,p).[41] Restricted calculations were performed, as all relevant species were closed shell molecules. All reported energies include zero-point energy, use pure d orbitals, and are gas-phase Gibbs free energies derived from the equation $\Delta G = \Delta H - T\Delta S$ using the calculated ΔH and ΔS terms at $T = 298.15$ K.

Preparation of Aldimine Substrates. The following method[20] was utilized to synthesize the aldimine substrates, which are known compounds. A total of 200 mmol of an aldehyde was dissolved in 80–200 mL of methanol. To this, 100 mmol of liquid diamine was added and the reaction was shaken for 16 h. In the case of solid formation (salophen), the solid was isolated by filtration, washed with 100–200 mL of methanol, and dried in vacuo. If no solid formed (*N*-benzylideneaniline and *N*-benzylidenetoluidine), the solution was concentrated by rotary evaporation. A dichloromethane extraction was performed and the organic layer was dried over magnesium sulfate. The slurry was filtered and the filtrate concentrated by rotary evaporation. This yellow–orange oil can be used or higher purity aldimines can be prepared by short path distillation of the aldimine near 130–140 °C under high vacuum.

***N*-Benzylideneaniline (11).**[18] 90% yield. ^1H NMR ($CDCl_3$): δ 7.25 (m, 3H), 7.42 (m, 2H), 7.49 (m, 3H), 7.92 (m, 2H), 8.47 (s, 1H). ^{13}C NMR: δ 121.1, 126.2, 129.0, 129.1, 129.4, 131.7, 136.4, 152.3, 160.7. MS (ESI): *m/z* = 182 $[M + H]^+$. $C_{13}H_{11}N$ (181.09).

***N*-Benzylidenetoluidine (11-Me).**[18] 98% yield. ^1H NMR ($CDCl_3$): 2.45 (s, 3H), 7.25 (m, 4H), 7.55 (m, 3H), 7.98 (m, 2H), 8.54 (s, 1H). ^{13}C NMR: δ 21.3, 121.1, 129.0, 129.1, 130.1, 131.5, 136.1, 136.7, 149.8, 159.9. MS (ESI): *m/z* = 196 $[M + H]^+$. $C_{14}H_{13}N$ (195.10).

***N,N′*-Bis(salicylidene)-*o*-phenylenediamine (16, salophen).**[42] 95% yield. ^1H NMR ($CDCl_3$): δ −1.90 (s, 2H), 6.94 (t, 2H, $^3J_{HH}$ = 7.5 Hz), 7.07 (d, 2H, $^3J_{HH}$ = 7.5 Hz), 7.24 (m, 2H), 7.35 (m, 2H), 7.40 (m, 4H), 8.64 (s, 2H). ^{13}C NMR: δ 117.6, 119.1, 119.4, 119.8, 127.9, 132.5, 133.5, 142.6, 161.5, 163.8. MS (ESI): *m/z* = 317 $[M + H]^+$. $C_{20}H_{16}N_2O_2$ (316.35).

1,2,*N,N′*-Tetraphenylethylene-1,2-diamine (13).[18] A flask was charged with 18.12 g (100 mmol) of *N*-benzylideneaniline, 0.125 g (2.6 mmol) of NaCN, and 50 mL of *N,N*-dimethylformamide. The mixture was sparged with N_2 for 20 min and sealed with a rubber septum. The reaction was stirred for 24 h and then 100 mL of methanol was added. The solution was cooled to 0 °C. The resulting yellow solid was isolated by filtration. High vacuum-drying provided 13.0 g (71.8%) of a neon yellow–green solid. The product can be recrystallized from dichloromethane affording *E*-1,2,*N,N′*-tetraphenylethylene-1,2-diamine. The ^1H NMR ($CDCl_3$) spectrum at −50 °C indicates a

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nearly even mixture of *E* and *Z* isomers: δ 5.73 (s, 1H), 5.77 (s, 1H), 6.56 (m, 4H), 6.77 (m, 2H), 7.10−7.34 (m, 12H), 7.56 (d, 2H, $^3J_{HH}$ = 8.4 Hz). The ^{13}C NMR ($CDCl_3$) spectrum at −50 °C indicates a nearly even mixture of *E* and *Z* isomers: δ 116.0, 116.1, 119.0, 119.1, 126.8, 127.3, 128.0, 128.2, 128.5, 128.7, 129.2, 129.4, 129.5, 130.5, 136.6, 136.8, 143.8, 145.6 MS (ESI): m/z = 363 [M + H]$^+$. $C_{26}H_{22}N_2$ (362.47). X-ray crystallography (SM18): Green plates were grown by slow evaporation of a dichloromethane solution. Crystal data: monoclinic, $P2_1/c$, a = 11.091(7) Å, b = 8.924(5) Å, c = 19.781(12) Å, α = 90°, β = 101.359(11)°, γ = 90°, V = 1919.4(19) Å^3, Z = 4, T = 110(2) K, R_1 (on F_0) = 0.0574, wR_2 (on F_0^2) = 0.1340, GOF = 1.008 for 225 parameters and 3333 unique data.

1,2,-Diphenyl-*N*,*N*′-di-(*p*-methylphenyl)-ethylene-1,2-diamine (13-Me₂).[18] A flask was charged with 20.0 g (102.5 mmol) of *N*-benzylidenetoluidine, 1.0 g (20.4 mmol) of NaCN, and 50 mL of *N*,*N*-dimethylformamide. The mixture was sparged with N_2 for 20 min and sealed with a rubber septum. This was stirred for 24 h and then 100 mL of methanol was added. The solution was cooled to 0 °C. The resulting yellow slurry was filtered. High vacuum-drying provided 13.4 g (67.0%) of a neon yellow solid. The product can be recrystallized from dichloromethane affording *E*-1,2-diphenyl-*N*,*N*′-di-(*p*-methylphenyl)-ethylene-1,2-diamine. The ^{1}H NMR ($CDCl_3$) spectrum at −60 °C indicates a 90:10 mixture of *E* and *Z* isomers. Major isomer: δ 2.22 (m, 6H), 5.71 (m, 2H), 6.47 (d, 4H, $^3J_{HH}$ = 5.1 Hz), 6.95 (m, 4H), 7.26 (m, 6H), 7.55 (d, 4H, $^3J_{HH}$ = 7.5 Hz). ^{13}C NMR ($CDCl_3$, −60 °C): δ 20.6, 115.6, 127.1, 127.5, 127.8, 128.0, 128.8, 129.4, 136.1, 142.5. MS (ESI): m/z = 391 [M + H]$^+$. $C_{28}H_{26}N_2$ (390.21). X-ray crystallography (SM81): Neon yellow needles were grown by slow evaporation of a dichloromethane solution. Crystal data: orthorhombic, $Fdd2$, a = 16.5867(17) Å, b = 44.319(6) Å, c = 5.7826(6) Å, α = 90°, β = 90°, γ = 90°, V = 4250.8(8) Å^3, Z = 8, T = 110(2) K, R_1 (on F_0) = 0.0430, wR_2 (on F_0^2) = 0.1024, GOF = 1.046 for 138 parameters and 1534 unique data.

(±)-2,3-Di-(2-hydroxyphenyl)-1,2-dihydroquinoxaline (17).[20] A flask was charged with 11.60 g (36.7 mmol) of *N*,*N*′-bis(salicylidene)-*o*-phenylenediamine, 2.00 g (40.8 mmol) of sodium cyanide, 1.50 g (4.06 mmol) of tetra-*n*-butylammonium iodide, 100 mL of dichloromethane, and 100 mL of water. The reaction mixture was refluxed for 64 h. The solid that formed at the interface of the two phases was isolated by suction filtration and dried in vacuo to yield 6.50 g (56.0%) of product. Single crystals can be grown by slow evaporation of a toluene or acetone solution. ^{1}H NMR (acetone-d_6, RT): δ −0.22 (s, 1H), 2.88 (s, 1H), 6.12 (broad s, 1H), 6.34 (m, 1H), 6.17 (m, 4H), 6.97 (m, 4H), 7.30 (m, 2H), 7.46 (m, 1H), 9.12 (broad s, 1H), ^{13}C NMR (acetone-d_6, RT): δ 46.9, 114.5, 114.6, 115.8, 117.8, 117.9, 118.2, 118.6, 120.2, 126.1, 126.2, 128.01, 128.04, 128.2, 139.2, 129.7, 132.66, 132.71, 153.3, 162.7. ^{1}H NMR ($Cl_2DCCDCl_2$, 130 °C): δ 3.50 (s, 1H), 7.55 (s, 1H), 7.89 (d, 1H, $^3J_{HH}$ = 9.0 Hz), 8.11 (m, 4H), 8.37 (m, 4H), 8.65 (m, 3H), 9.13 (broad s, 1H), 9.39 (broad s, 1H). ^{13}C NMR ($Cl_2DCCDCl_2$, 130 °C): δ 49.8, 116.6, 117.7, 119.7, 119.9, 120.0, 120.8, 121.1, 123.1, 127.9, 129.3, 130.4, 130.5, 131.1, 132.3, 133.0, 133.5, 134.2, 137.0, 164.1. MS (ESI): m/z = 317 [M + H]$^+$. $C_{20}H_{16}N_2O_2$ (316.35). X-ray crystallography (SM11): Orange−red blocks were grown by slow evaporation of a toluene solution. Crystal data: monoclinic, $P2_1/n$, a = 9.708(2) Å, b = 15.970(4) Å, c = 11.254(3) Å, α = 90°, β = 115.496(3)°, γ = 90°. V = 1574.9(6) Å^3, Z = 4, T = 110(2) K, R_1 (on F_0) = 0.0557, wR_2 (on F_0^2) = 0.1015, GOF = 1.056 for 229 parameters and 3553 unique data. A second crystal from a separate preparation was grown by slow evaporation of an acetone solution. An essentially identical X-ray structure was determined.

Acknowledgment. The authors thank the Robert A. Welch Foundation (no. A-1537) and the donors of the Petroleum Research Fund (no. 39671-G1), administered by the American Chemical Society, for support of this research. We thank the staff at the supercomputing facilities and the Laboratory for Molecular Simulations at Texas A&M University for quantum chemical calculation support. Lisa M. Pérez and Chad Beddie are thanked for their valuable quantum chemical calculation insights. A.K.J. gratefully acknowledges the NSF-REU program for a 2003 undergraduate summer fellowship.

Supporting Information Available: Compound characterization data, including NMR spectra, X-ray crystallographic data (**13**-*E*, **13**-Me₂-*E*, and **17a**), DFT zero-point energies, and Cartesian coordinates for all relevant computationally studied species. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051102G