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Highly Stable Keto-Enamine Salicylideneanilines

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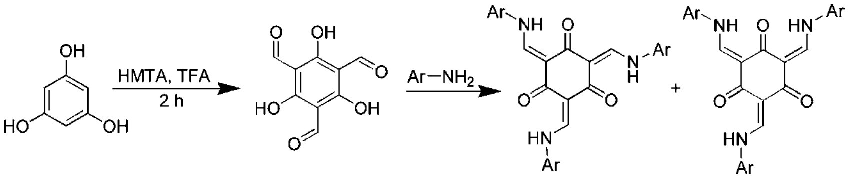
ABSTRACT

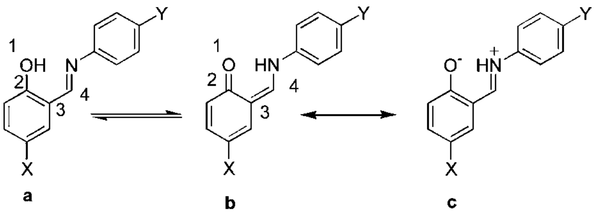


Highly stable NH salicylideneanilines have been prepared by reaction of 1,3,5-triformylphloroglucinol with aniline derivatives. The NH form was confirmed by X-ray crystallographic data, as well as by NMR studies. A convenient one-step synthesis of triformylphloroglucinol is also reported.

Proton tautomerism is central to several fields of chemistry and biochemistry and plays a role in pharmaceutical action, enzyme activity, and the stabilization of base pairs in duplex DNA.[1,2] *N*-Salicylideneanilines (**1**) are an interesting class of compounds possessing an OH···N hydrogen bond. These compounds are often thermo- and photochromic, undergoing reversible proton transfers (tautomerism) in the solid state (e.g., **1a** $\rightleftharpoons$ **1b**).[3]

As proton transfer in these systems causes a change in optical properties, these molecules are candidates for optical switches and storage devices.[4] There have been many studies of proton transfer in the solid-state and in solution.[5]

Generally, the enol-imine (OH) form (i.e., **1a**) is the most stable form at room temperature but is in equilibrium with the keto-enamine (NH) form (i.e., **1b**).[6] As a result, the OH form of *N*-salicylideneanilines has been well-characterized, but, until recently, no NH form had been structurally characterized.[7,8] Ogawa has undertaken low-temperature X-ray diffraction experiments of **2** and observed that at 15 K, the NH form (**2b**) is present.[8,9] However, as the bond lengths more strongly resemble those of **2a** than those calculated (DFT) for the quinoidal form **2b**, the authors conclude that **2c** is the canonical structure that is dominating



1 (X = H; Y = H)
2 (X = Cl, Y = OH)

Figure 1. Tautomerization of compounds **1** and **2** showing the two canonical structures contributing to the resonance structure of the NH form. Atomic numbering is for use in Table 1.

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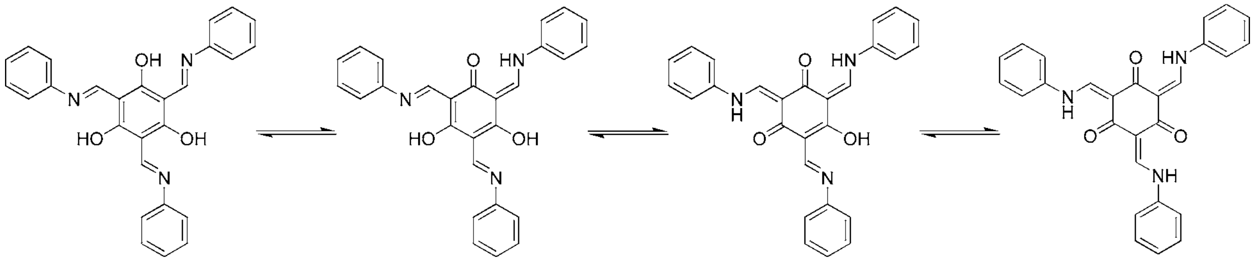


3a **3b** **3c** **3d**

Figure 2. Structures of the tautomers of tris(*N*-salicylideneaniline) **3a**.

in the crystalline state. The relative contributions of the quinoidal (**1b**) and zwitterionic (**1c**) canonical structures to the resonant structure of *N*-salicylideneanilines have been an issue of investigation.[10]

Here, we report the first structural characterization of the NH form of a *N*-salicylideneaniline that resembles the quinoidal form predicted by DFT calculations in the gas phase.

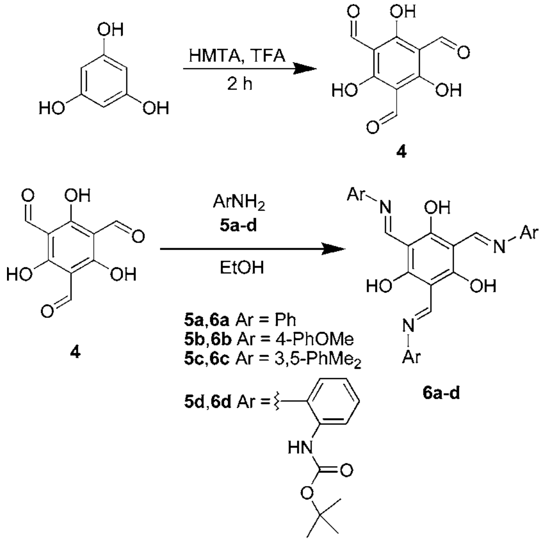
We identified tris(*N*-salicylideneaniline) **3a** (Figure 2) as an intriguing target since it might undergo multiple proton transfers and serve as a multistep photochemical switch. In the case of **3**, there are four tautomers that could possibly be addressed. To initiate this work, 1,3,5-triformylphloroglucinol (**4**) was required. Although this molecule was previously prepared in seven steps from 1,3,5-trichlorobenzene, with an overall yield of 21%, the product was not characterized.[11] We discovered that reaction of phloroglucinol with hexamethylenetetramine (HMTA) in trifluoroacetic acid (Duff formylation[12]) afforded compound **4** in one step (Scheme 1). Although the yield is low (14%), the reaction is simple, takes only 2 h, and affords a crude product with ca. 99% purity. We have attempted to increase the yield by varying the reaction conditions (time, temperature) but have not found improved conditions. Moreover, drying of the phloroglucinol does not significantly affect the yield.

Compound **4** is remarkably stable. It melts at 198−200 °C and can be sublimed at 120 °C under vacuum ($\sim 10^{-3}$ Torr). Its ^{1}H NMR spectrum shows only two singlets at 10.14 and 14.10 ppm (CDCl$_3$), assigned to the aldehyde and phenol, respectively. The large downfield shift of the phenolic proton is consistent with strong intramolecular hydrogen-bonding in the molecule. The IR spectrum of **4** shows an intense absorption at 1641 cm^{-1}, characteristic of an aldehyde.

Tris(*N*-salicylideneaniline) derivatives **6a**−**c** were prepared in 52−62% yield by the reaction of compound **4** with an excess of aniline derivative **5a**−**c** in refluxing ethanol (Scheme 1). The IR spectra of the yellow-orange, fluorescent compounds **6a**−**c** all confirmed the disappearance of the aldehyde.

^{1}H NMR spectra of **6a**−**c** were surprisingly complicated (Figure 3). Whereas singlets were expected for the imine and phenol in the OH form, the spectra showed multiple peaks between 8.5−9.0 and 12.8−13.5 ppm. ^{1}H−^{1}H COSY spectra elucidated coupling between doublets in these two regions. The ^{1}H NMR spectra for **6a**−**c** show that only the

Scheme 1. Synthesis of **4** and **6**



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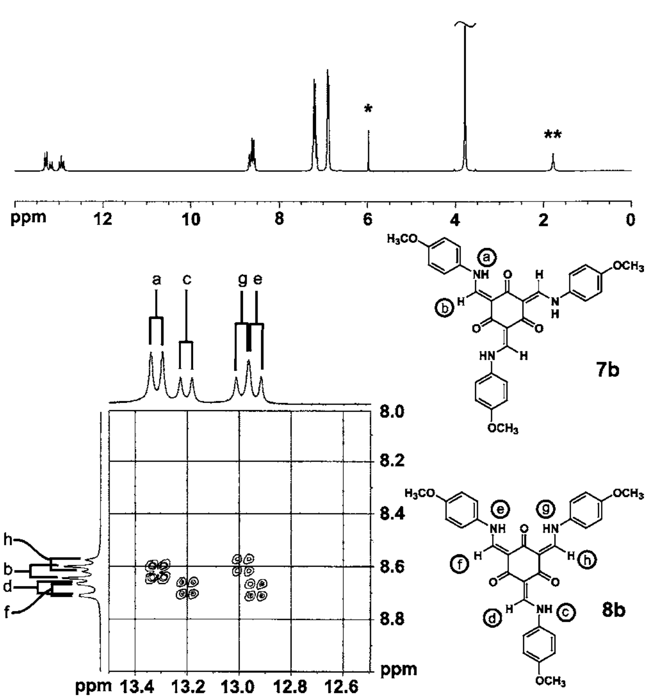

Figure 3. ^{1}H NMR spectrum of **6b** (top) and ^{1}H−^{1}H COSY NMR spectrum (bottom; $(CDCl_2)_2$) showing coupling between vinylic and NH protons. At the right are the two structures (with C_{3h} and C_S symmetry) evident in the ^{1}H NMR spectrum. (* = $CHCl_2CDCl_2$; ** = water in the NMR solvent).

all-keto-enamine (NH) form of **6a**−**c** is present, in a mixture of two geometric isomers (**7** and **8**), as shown in Figure 4. In each compound, coupling is observed between the enamine proton and the NH ($^3J_{HH} \approx 13.5$ Hz).[13]

^{13}C NMR spectra of **6a**−**c** showed the carbonyl resonance of the central ring at ca. 185 ppm, characteristic of the keto isomer.[5c,14] Moreover, the peaks assigned to the =CNH and C=O groups of the two geometric isomers **7** and **8** could be resolved.

We also prepared the ^{t}BOC-protected compound **6d** by reacting **4** with **5d**.[15] Compound **6d** was purified by recrystallization and characterized. To confirm the structure of **6d**, crystals suitable for single-crystal X-ray diffraction were obtained from slow evaporation of **6d** in 1:1 CH_2Cl_2/hexanes.

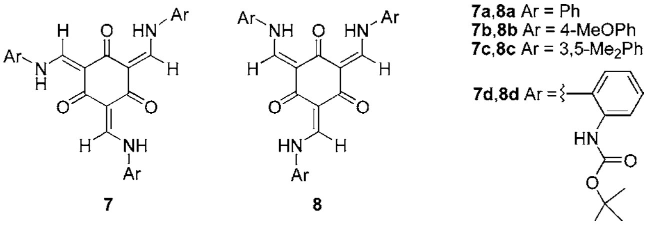

Figure 4. There are two possible geometric isomers of each compound **6a**−**d** in its keto-enamine (NH) form, **7** and **8**, with symmetry C_{3h} and C_s, respectively.

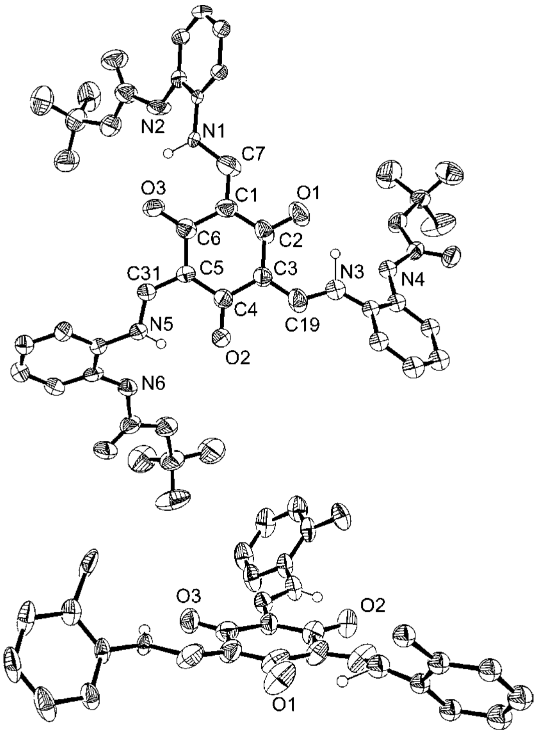

Figure 5. Molecular structure of compound **6d** shown with thermal ellipsoids at 50% electron density. All hydrogen atoms, other than those bonded to N1, N3, and N5, have been omitted. In the bottom structure, the ^{t}BOC groups have been removed for clarity.

The molecular structure of **6d** is shown in Figure 5.[16,17] Notably, the compound is the keto-enamine tautomer of **6d** (i.e., **7d**), a cyclohexanetrione with approximately C_{3h} symmetry in the central ring.[18] The central C_6 ring is flat (within error), with average C−C bond lengths of 1.45(1) Å, considerably longer than the average C−C bond length in benzene (1.38 Å). Moreover, the C−O bond lengths (avg = 1.256(8) Å) are more characteristic of ketones than C−OH bonds. As a virtue of the central cyclohexanetrione present in compounds **7** and **8**, these molecules may be viewed as 1,3,5-trisoxa[6]radialenes;[19] this motif has been reported previously in only a couple of cases with sulfur substituents.[20]

Unlike other *N*-salicylideneanilines that typically exist in equilibrium between two tautomers in solution and as a

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[13] Yields reported are of purified, isolated product. ^{1}H NMR spectra of the supernatant solution from the reaction of **4** with **5b** appeared identical to the isolated product plus excess **5b**. There was no evidence for imine, aldehyde, or other resonances that would be expected for the OH form **6b**.

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[16] Crystal data: FW = 782.88, orthorhombic, *Pccn*; $a = 11.2522(5)$ Å, $b = 22.989(1)$ Å, $c = 37.807(2)$ Å; $V = 9779.9(7)$ Å^3, $Z = 8$, $T = -100(1)$ °C, μ(Mo Kα) = 0.76 cm^{-1}, 8537 observed reflections, 572 variables, $R = 0.156$, $R_w = 0.292$, GOF = 0.92.

[17] X-ray structure shows positional disorder in the ^{t}BOC groups and one of the phenylenediamine rings. The central ring shows no disorder, and its dimensions are reliable.

[18] Positions of the H atoms between O1, O2, O3 and N3, N5, N1 were refined isotropically and found to be localized on the N-atoms.

mixture of the two tautomers in the solid state, **6a−d** are only observed in the NH form (**7** and **8**). We have not observed the imine tautomers (OH form) of **6a−d** in our experiments. As the formation of the cyclohexanetrione core in **7** or **8** is accompanied by loss of aromaticity in the central benzene ring, it must be accompanied by a net stabilization from other factors. This stabilization likely arises from the relatively large basicity of the nitrogen vs the phenolic oxygen.

Ab initio DFT calculations were performed on the OH and NH forms of **6a**. Calculations show that the keto form (**7a**) is stabilized relative to the enol form (**6a**) by $\Delta H_f = -75$ kJ/mol.[21] Moreover, the calculations indicate that the planarity of the central core is maintained by hydrogen bonding. With respect to the bond lengths and angles in the core, the calculated dimensions of **7a** are very similar to those calculated for the quinoidal tautomers **1b** and **2b** (Table 1). While the bond lengths for **2** at 15 K by Ogawa et al. are best explained as a zwitterionic structure (**2c**), our X-ray diffraction experiment (173 K) indicates that **6d** is very similar to that predicted for the quinoidal structure (**2b**).

With the exception of **6d**, the two geometric isomers of **6a−c** (i.e., **7a−c** and **8a−c**) were both present and could not be separated by chromatography or recrystallization. They do not interconvert on the NMR time scale even when heated to 120 °C in aprotic solvent. This is surprising since a simple proton transfer from NH to O would facilitate this isomerization. From the ^{1}H NMR spectrum for **6b**, the ratio of the C_{3h} (**7b**) to C_S (**8b**) isomers present is ca. 1:1.4 vs the 1:2 ratio expected in a statistical mixture. Calculations indicate that the C_{3h} isomer is more stable than the C_S isomer, but the difference is small. Due to the tremendous stability of the NH form in the tris(*N*-salicylideneaniline), these compounds are not readily interconverted between their various tautomeric forms in aprotic solvents. In methanol-d_4, the ratio of **7** to **8** changes, indicating that there is slow interconversion between the geometric isomers, but still only the NH form is observed by NMR spectroscopy.

Table 1. Experimental and Calculated Dimensions of Enol-enamines **2** and **6**

compound	method	T (K)	tautomer	distance (Å)[a] O1−C2	C2−C3	C3−C4
2	XRD[b]	15	NH	1.310(1)	1.433(2)	1.425(1)
2	DFT[b]	0	OH	1.341	1.423	1.452
2	DFT[b]	0	NH	1.263	1.469	1.400
6a[c]	DFT[d]	0	OH	1.330	1.421	1.443
6a	DFT[d]	0	NH	1.256	1.461	1.386
6d	XRD[d]	173	NH	1.256(8)	1.452(8)	1.38(1)

[a] Atom labels from Figure 1. [b] From ref 8. [c] Same as **3**. [d] From this study.

In summary, we have obtained the first X-ray diffraction evidence of a *N*-salicylideneaniline locked in the NH form that is consistent with the gas-phase quinoidal structure. We have also discovered a convenient route to triformylphloroglucinol, a molecule that leads to interesting conjugated hetero[6]radialenes upon condensation with aromatic amines.

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Supporting Information Available: Experimental details for the synthesis of **4** and **6a−d** and X-ray crystallographic data for **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Calculated with Spartan at the B3LYP/6-31G* level. Semiempirical AM1 and PM3 calculations gave $\Delta H_F = -96.0$ and -25.0 kJ/mol (keto more stable), respectively. AM1 is known to give good estimates of energies where strong hydrogen bonding is present, as in compounds **6**. Geometries predicted by all three methods were similar.