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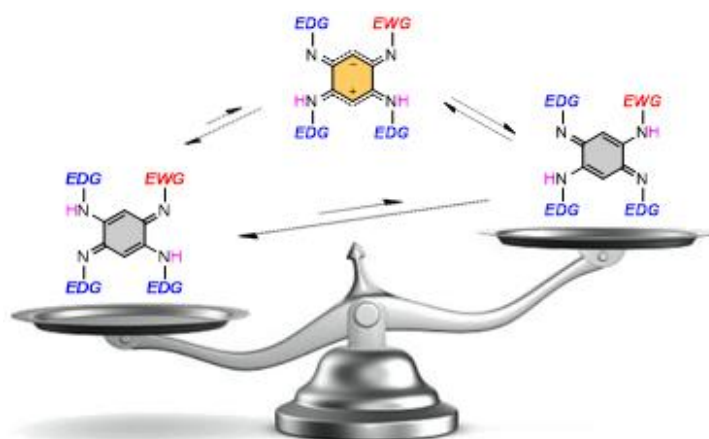
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Stabilization of a 12- π Electrons Diamino-Benzoquinonedimine Tautomer

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Abstract. The first example of diamino-benzoquinonedimine bearing both electron-donating and electron-withdrawing groups on the same 6- π electron subunit was synthesized using a straightforward one pot strategy. Photophysical analysis combined with theoretical calculations demonstrates that this unique substitution pattern is efficient to favour the establishment of a single tautomeric structure in solution.

Introduction

Possessing numerous applications in different fields ranging from biology to physics, quinoidal molecules are in the limelight of daily chemistry life. Indeed, they are used for instance as organic oxidizing agents,^{1,2} pharmaceutical drugs or supplement,^{3,4} as well as dyes and pigments.⁵ Among the different classes of quinones, 2,5-diamino-1,4-benzoquinonediimines (QDIs) display fascinating optical properties due to the so-called “coupling principle”.^{6–8} This postulate results from the specific distribution of their overall 12- π electrons that can be considered as two electronically independent 6- π electron subsystems, chemically connected by two C–C single bonds, giving rise to fascinating optical properties upon protonation.⁸ One of the most striking feature of these 12- π electron QDIs of type 1 (

Fig. 1) – substituted with hydrogen atoms or alkyl electron-donating groups (EDG) – is their ability to undergo a fast intramolecular double proton transfer. This results in the formation of two degenerate tautomers in equilibrium, **c-1** and **c'-1**, generating a high (pseudo-)symmetric structure in solution which was established by kinetic NMR studies.^{11,8,9,10,11} More recently, we described a series of type 2 asymmetric *N*-substituted QDIs featuring tuneable aryl electron-withdrawing functions (Fig. 1). The subtle variation of the electronic richness allows controlling the intramolecular proton transfer, that now induces an equilibrium between uncharged canonical (**c-2**) and zwitterionic (**z-2**) forms,^{12,13,14} contrasting with the fast double proton transfer taking place in QDIs of type 1. In practice, the formation of a stable ground-state conjugated zwitterion **z-2** takes place in aprotic polar solvents such as DMF or DMSO, leading to drastic colour changes. Obviously, a further step would be to control the H-transfer by selectively stabilizing one uncharged tautomer **c** or **c'** in solution. In this context, the access to QDIs of type 3 bearing both EWG and EDG on the same 6- π electrons subunit is specifically appealing because the electronic density difference between the two nitrogen atoms should lead to unique properties. Herein, we describe by serendipity the first member of a new class of QDIs (type 3), and

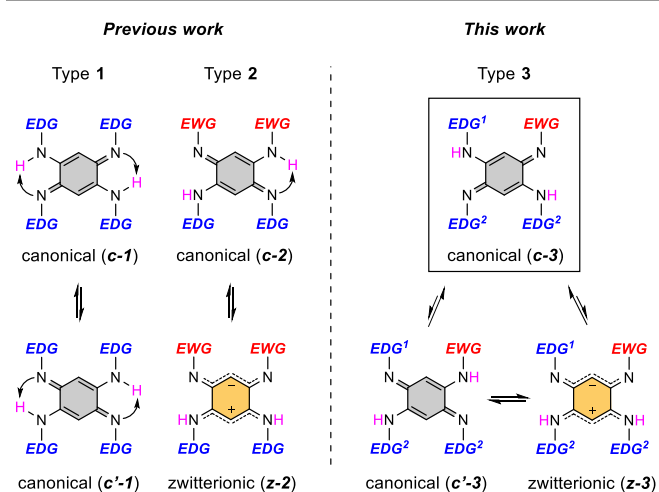


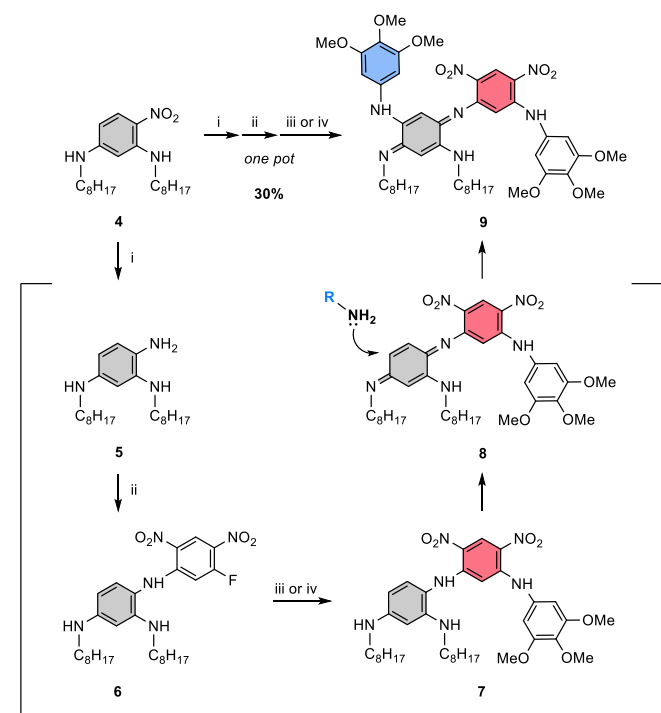
Fig. 1. Structures of 12- π electrons QDIs bearing different substituents. EDG = Electron-Donating Groups; EWG = Electron-Withdrawing Groups.

its spectral properties under various conditions. The combined experimental and theoretical studies clearly demonstrate the high chemical stability of **c-3** in solution, almost perfectly preventing the formation of the uncharged (**c'-3**) and/or zwitterionic (**z-3**) tautomers.

Results and discussion

Synthesis

In the course of our study on new synthetic route to access phenazine rings, we isolated an unexpected compound, which turned out to be QDI **9**. Its story started by the nucleophilic substitutions (S_NAr) of 3,4-difluoronitrobenzene (DFNB), with octylamine in the presence of *N,N'*-diisopropylethylamine (DIPEA) at 140 °C for 3 hours which afforded compound **4** in 96% yield (Scheme 1).¹⁵ Afterwards, the NO_2 function of **4** was reduced under a 40 bars H_2 atmosphere in the presence of Pd/C. Then, the reduced compound **5** was mixed with 1,5-difluoro-2,4-dinitrobenzene for 1 hour. Subsequently – without any treatment – the latter mixture was exposed to an excess of 3,4,5-trimethoxyaniline (TMA) (2.1 equiv.) and DIPEA (2.1 equiv.) under aerobic conditions and for 10 days (oversight) to afford the desired QDI **9** with an overall 30% yield (one pot: 3 steps). Noteworthy, aerobic conditions appeared essential for the synthesis of **9**. Indeed, the latter could not be isolated when carrying the same reaction sequence under an inert atmosphere, even at higher temperatures.[‡] Assuming this observation, a global plausible reaction mechanism can be considered starting from triaminobenzene **5**. The first step



Scheme 1. Chemical synthesis of QDI **9**. i) H_2 (autoclave 40 bars), Pd/C, THF/MeOH, 12 h, 25 °C; ii) 1,5-difluoro-2,4-dinitrobenzene (1 equiv.), DIPEA (1 equiv.), THF/MeOH, 1 h, 0 to 25 °C; iii) 3,4,5-trimethoxyaniline (2.1 equiv.), DIPEA (2.1 equiv.), THF/MeOH, aerobic conditions, 10 days, 25 °C or iv) 3,4,5-trimethoxyaniline (2.1 equiv.), DIPEA (2.1 equiv.), THF/MeOH, reflux 12 h, then MnO_2 (10 equiv.) 12 h, 25 °C. R = 3,4,5-trimethoxyaniline. Compounds into brackets were not isolated.

would consist in the formation of **6** through a mono-substitution of 1,5-difluoro-2,4-dinitrobenzene by **5** followed by fluorine atom substitution of **6** by TMA *via* a S_NAr reaction. At this stage, the TMA EDG moiety may enhance the electronic richness of **7** which enable the oxidation of the triaminobenzene ring into QDI **8**. Interestingly, the upper part of **8** can be considered as an α,β -unsaturated imine bearing EWG and consequently as a "Michael acceptor" Therefore, QDI **9** is finally obtained after a 1,4-Michael-type nucleophilic addition of TMA, followed by an oxidation of the obtained adduct (see Scheme 1).^{16,17} We optimized the reaction conditions to reduce the "necessary" 10 days of reaction. After checking the formation of **6** by TLC, TMA and DIPEA (2.1 equiv. each) were added and the mixture refluxed for 12h to reach complete formation of **7**. Afterwards, addition of MnO_2 (10 equiv.) speed up the final oxidation steps as compound **9** was isolated in a 28% overall yield in 36 h. The establishment of **9** canonical form could be demonstrated by combining 1H and ^{15}N NMR spectroscopy. The 1H NMR spectrum of **9** in $CDCl_3$ shows the presence of two non-aromatic signals at 5.39 and 5.71 ppm both integrating for a single H atom. These values match perfectly with the two olefinic proton's chemical shifts belonging to the quinonediimine subunits. We then performed 1H - ^{15}N HMBC NMR experiment in $DMSO-d_6$, from which a correlation between an sp^3 hybridized nitrogen¹⁸ and aromatic protons of the trimethoxybenzene moiety (blue cycle in Scheme 1) can be observed (Fig. S6, ESI⁺) at $\delta^{15}N$ - δ^1H of 103.2-6.58 and 103.2-6.40 ppm. This result is consistent with the presence of a single tautomer of QDI **9**, as drawn in scheme 1.

Electronic absorption and electrochemistry

We first evaluated the redox properties of **9** in DCM by cyclic voltammetry (see Fig. S11, ESI⁺). Its cyclic voltammogram presents two irreversible oxidations at 0.177(1e) V and 0.725(2e) V vs. Fc/Fc^+ whereas quinone of type **1** and **2** exhibit only one oxidation process. The first oxidation process being easier by 0.16-0.50 V compared to type **1** and **2** quinones.^{12,19} As for the reduction process, **9** shows an irreversible one electron reduction at -1.39 V vs Fc/Fc^+ which is in the range of the one observed for quinone of type **2**.

The electronic absorption of QDI **9** in DCM shows a broad and intense absorption band centred at 374 nm (Fig. 2). The lack of absorption band beyond the blue region strongly suggests the presence of the canonical form in solution. Since solvent polarity can trigger the establishment of zwitterionic ground

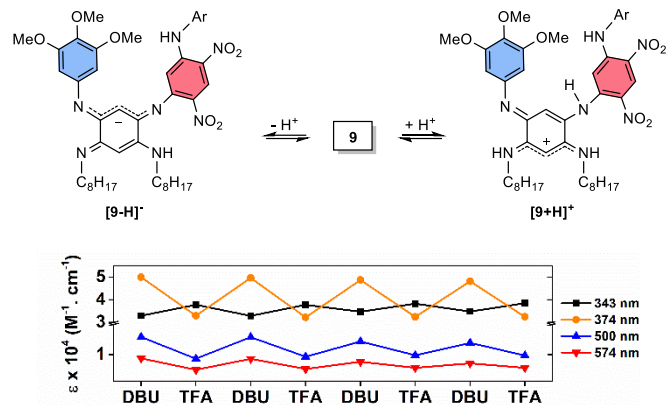


Fig. 3. Structures generated upon protonation or deprotonation of quinone **9**. Ar = 3,4,5-trimethoxyphenyl. Plot of ϵ changes at different wavelength (343, 374, 500 and 574 nm) vs the addition of DBU (20 equiv.) followed by iterative [TFA (40 equiv.) / DBU (40 equiv.)] additions.

state structures in EWG substituted QDI,^{12,13} the solvatochromism has been investigated (Fig. 2A). The weak effect of solvent polarity and proticity can be clearly seen when looking at the maximum absorption wavelength in the UV region which shows almost no change of both wavelength and molar extinction coefficient when going from DCM to DMF (see Table S1, ESI⁺). However, a subtle change can be detected in DMSO. Indeed, a low energy band centred at 657 nm appears with a small but non-trifling molar absorption coefficient of *ca.* 750 $M^{-1} cm^{-1}$, this band being the typical signature of a zwitterionic form in solution (*vide infra*). Since QDIs are known to be easily protonated in solution,⁸ we studied the pH influence on the absorption spectra of **9**. Addition of an excess of trifluoroacetic acid (TFA) or HCl (Fig. 2B) induces the emergence of a redshifted absorption band centred at 550-555 nm (ϵ *ca.* 7800 $M^{-1} cm^{-1}$). This change results from the 6- π electron delocalization within the cyanine-like cationic subunit of the mono-protonated QDI [**9+H**]⁺ (Fig. 3).¹² Conceivably due to the electron-poor character of the second 6- π electron upper subunit, it was impossible to reach the di-protonated state [**9+2H**]²⁺ even with a large excess of TFA.¹² Increasing the pH with a large excess of triethylamine ([TEA] = 0.1 M; pK_a = 10) in DCM does not yield any significant change. This is not the case in DMSO as a slight change in the electronic absorption is monitored, *i.e.*, the appearance of a shoulder between 470-600 nm. Addition of a stronger base, namely 1,8-diazabicyclo[5.4.0]undec-7-ene ([DBU] = 0.1 M; pK_a = 12) in

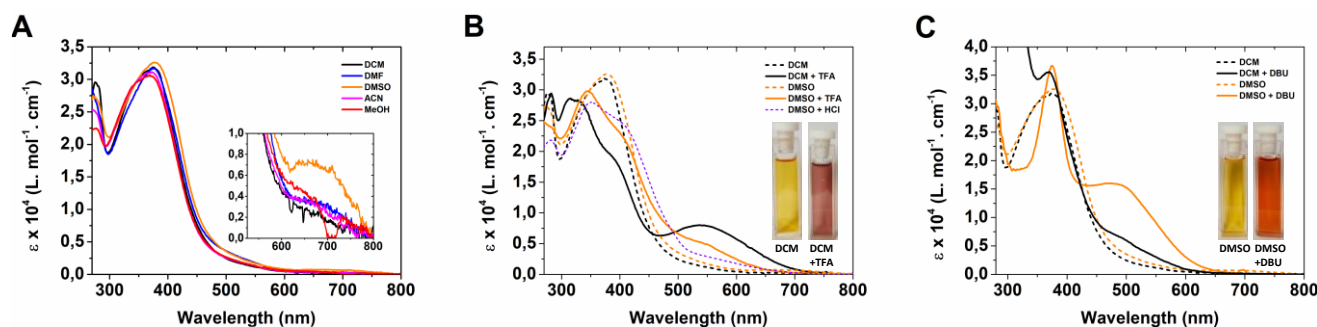


Fig. 2. Electronic absorption spectra of quinone **9** (10^{-5} M) under different conditions. A: solvatochromism study (DCM = dichloromethane, ACN = acetonitrile, DMF = *N,N*-dimethylformamide, DMSO = dimethylsulfoxide). B: protonation study in DCM and DMSO with TFA (0.1 M) or HCl (100 equiv. added in DMSO only for miscibility reasons); C: deprotonation study in DCM and DMSO with DBU (0.1 M).

DMSO leads to an instantaneous colour change (Fig. 2C). Such coloration results from the appearance of an absorption band at 474 nm ($\epsilon \sim 16\,000\text{ M}^{-1}\text{ cm}^{-1}$) and is due to the $[\mathbf{9-H}]^-$ species stemming from deprotonation of the QDI. Moreover, as can be seen in Fig. 3 the deprotonation and protonation processes going from $[\mathbf{9-H}]^-$ to $[\mathbf{9+H}]^+$ is fully reversible.

From these results, we can extract that in solution, the canonical form of **9** is highly predominant, while a small fraction of zwitterion could be formed in DMSO. However, a question remains: when attached to the same subunit, are EDG and EWG groups favouring one of the three possible tautomers of **9**? To answer this question we performed theoretical calculations.

Theoretical calculations

To perform our calculations, we have used DFT and TD-DFT, accounting for solvent effects (DCM) using the well-known Polarizable Continuum Model (PCM) and replacing the alkyl chains C_8H_{17} by methyl groups for the sake of computational time (see the ESI[†] for the detailed protocol). For **9**, three isomers can be envisaged: two non-equivalent canonical tautomer **c-9** and **c'-9**, as well as a possible zwitterionic form **z-9** (Fig. 4). Given the side groups high flexibility of those structures, many conformers can be envisaged. First, let us consider only the two canonical structures **c-9** and **c'-9** that dominate experimentally: six conformers have been identified for each form (see Fig. S12, ESI[†]). Clearly, the theoretical calculations predict that the **c-9** type structures are largely dominant in solution, as they represent more than 95% of the total population. The asymmetry induced by the EWG moiety has clearly induced directionality in the quinoidal form, absent in type **1** QDIs. Let us now focus on the spectral features of the most stable canonical conformer **c-9**. TD-DFT returns the first three excited states at 472 nm ($f = 0.034$), 376 nm ($f = 0.170$) and 365 nm ($f = 0.624$). The first weakly allowed transition is responsible for the long absorption tail at long wavelength (Fig. 2) whereas the two other transitions correspond to the strong absorption band experimentally recorded at 374 nm. For all these three transitions, the orbital mix provided by TD-DFT is especially complex. Consequently, we have turned to electron density difference (EDD) plots to analyse the nature of these transitions (Fig. 5). It is clear that the first transition is a $\pi-\pi^*$

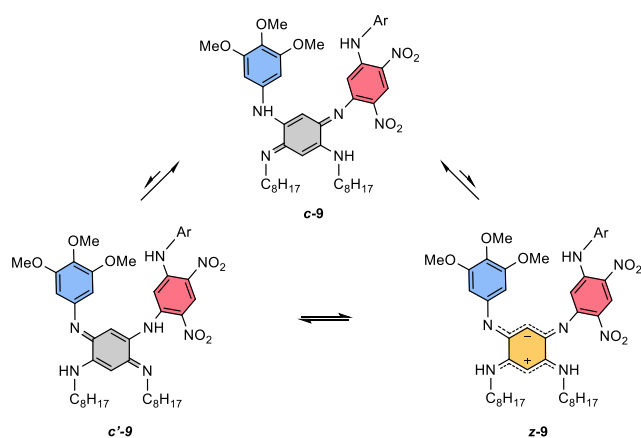


Fig. 4. Representation of the three neutral tautomeric structures of **9** considered in the calculations. Ar = 3,4,5-trimethoxyphenyl.

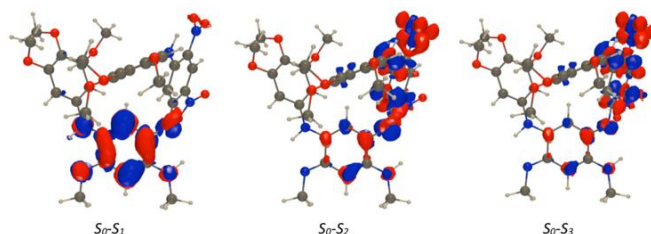


Fig. 5. EDD for the three lowest vertical transitions in **c-9**, located from left to right at 472, 376, and 365 nm. The blue and red regions represent zones of decrease and increase of electron density upon transition, respectively.

excitation localised on the quinoidal tetraamino fragment. By contrast, the second and third brightest transitions show a charge transfer (CT) character in which there is an electron transfer from the amino group to the nitro group in the *red cycle* (electron-withdrawing moiety diamino-dinitro-benzene, see Fig. 4).

We have also investigated the possible presence of zwitterions. The most stable **z-9** conformer is found to be less stable than the **c-9f** isomer by 1.3 kcal.mol^{-1} (Fig. S12, ESI[†]). Given our previous works,^{12,13} such 1.3 kcal.mol^{-1} value indicates that **z-9** is slightly less stable than **c-9**, so that its presence will depend on experimental conditions. Importantly, DFT predicts a much higher dipole moment for **z-9** (17.7 D) than in **c-9** (12.8 D), indicating that the former should be favoured in more polar environments, which is seen experimentally in DMSO. Moreover, TD-DFT predicts that **z-9** should show a moderately intense and redshifted CT band, at 628 nm ($f = 0.177$), which is consistent with the UV-vis measurements (Fig. 2 and Fig. S13, ESI[†]). Considering the protonation study, four inequivalent tautomers can be envisaged for the mono-protonated species $[\mathbf{9+H}]^+$. Nonetheless, DFT calculations clearly indicate that one form will strongly dominates (Fig. S15 and related text in ESI[†]). This form is of type **c'-9**, with the protonation taking place on the sp^2 hybridized nitrogen bearing an octyl chain. For the most stable $[\mathbf{9+H}]^+$ form, TD-DFT returns for the lowest transition, a bright transition at 496 nm ($f = 0.291$). As compared to **9**, there is therefore a redshift, and a very large increase of intensity, which is qualitatively in agreement with experiment in which the long absorption tail found in DCM becomes a clear absorption band upon TFA addition (Fig. 2). We also envisaged a doubly-protonated structure, $[\mathbf{9+2H}]^{2+}$, for which only one tautomeric form can be written (see Fig. S12, ESI[†]). For this structure TD-DFT returns a significant absorption at 630 nm ($f = 0.139$), which is unseen when adding TFA experimentally, confirming that only mono-protonation takes place.

Conclusions

Previous studies on diamino-benzoquinonediimine chemistry essentially pointed out the equilibrium between possible tautomers in solution *i.e.*: (i) equilibrium between two (uncharged) canonical forms, and (ii) equilibrium between (uncharged) canonical and zwitterionic ones. We described here that, by tailoring the electronic properties of the N-substituents at the right place, a (uncharged) canonical tautomer could prevail in solution to the detriment of the zwitterionic form and over the other canonical tautomer. This

unique behaviour could be demonstrated thanks to the access of **9** through a one pot synthesis, and a combined photophysical and computational studies of the first QDI bearing both electron-donating and electron-withdrawing groups on the same 6- π electron subunit. Moreover, either cationic or anionic species could be formed in solution. We now wish to investigate this new type of QDI as ligand in coordination chemistry in order to finely tune the properties of the metal centres in the complexes.^{20,21}

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Notes and references

|| Study on azophenine with aryl (phenyl) groups.

‡ The reaction has been tentatively carried out at the boiling point temperature of THF (66 °C).

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