

First transamination reactions for the one-pot synthesis of substituted zwitterionic quinones†

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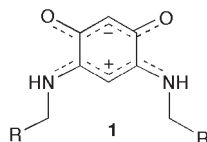
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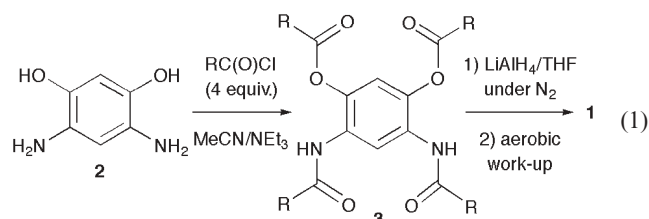
A new and very efficient one-pot synthesis, in water, of $6\pi + 6\pi$ electron zwitterionic benzoquinonemonoimines involves the first examples of transamination reactions in quinonoid chemistry and allows the introduction of functionalities to, and the fine-tuning of the properties of, a large family of molecules with interesting potential, both in supramolecular chemistry and as multidentate ligands in coordination chemistry.

The synthesis of quinonoid compounds is attracting considerable attention because of their implications in many areas of chemistry and biology.¹ More specifically, benzoquinonemonoimines occupy a central role in many commercial applications,² and have considerable potential in colour chemistry,^{2b} and in supramolecular, coordination and organometallic chemistry.^{3,4} We recently reported new N-substituted benzoquinonemonoimines of type **1** (R = alkyl or aryl), which are rare examples of zwitterions being more stable than their canonical forms.^{3–5}



The first member of this novel class of potentially anti-aromatic $6\pi + 6\pi$ electron molecules (R = *t*-Bu)³ immediately caught the attention of theoreticians owing to its fundamental importance.^{4,6} Furthermore, these zwitterions appear to be reagents of choice: (i) in organic chemistry,⁴ (ii) in coordination chemistry, as new ligands in the stepwise synthesis of polynuclear complexes,^{4,7} and (iii) in biochemistry as precursors to a bioinhibitors-related OH-substituted aminoquinone.⁵

A multistep procedure consisting of the reaction of diaminoresorcinol **2**·2HCl with RC(O)Cl in CH₃CN and excess NEt₃, to afford diamidodiester **3** in high yield [eqn. (1)], followed by their reduction with LiAlH₄ and an aerobic work-up, led to the zwitterions **1**.^{4,5}



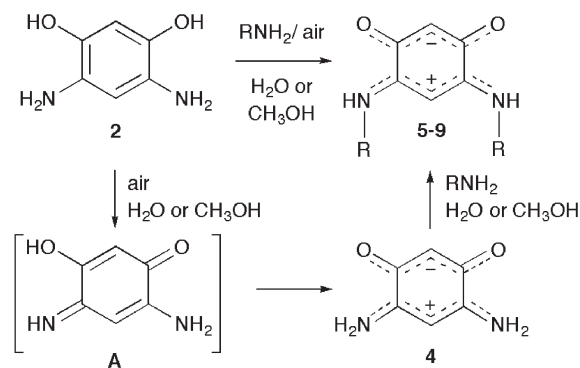
† Electronic supplementary information (ESI) available: synthetic and spectroscopic details and CIF files for the X-ray structures. See <http://www.rsc.org/suppdata/cc/b5/b501926e/>
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However, the preparation of a wide range of zwitterions could not be achieved owing to the need for highly reactive acid chlorides, in which the presence of other functional groups is limited, and whose reduction exclusively leads to $-NCH_2R$ substituted compounds. For further applications of this class of colorants, an atom-economic and “greener” synthesis (*i.e.* without organic solvent) would be of great interest. Here we report a new and extremely efficient preparation *in water* of new zwitterions, for which the N-alkyl substituent (*i.e.* the properties) can be easily varied by using an unprecedented transamination reaction on a quinonoid ring.

2·2HCl reacted smoothly with a large excess of various primary amines RNH₂ in water (or alcohol) at room temperature under air, to afford high yields of the corresponding zwitterions **5–9** which have been fully characterized (See ESI†) (Scheme 1).

In contrast to **7** and **8** which are only soluble in organic solvents, **5** is almost insoluble in most organic solvents but soluble in water owing to the presence of hydrophilic groups ($-OH$). In addition, **6** and **9** are soluble in both organic solvents and water. Therefore, we can now fine-tune the solubility of these molecules, which is a key point for their applications.⁸

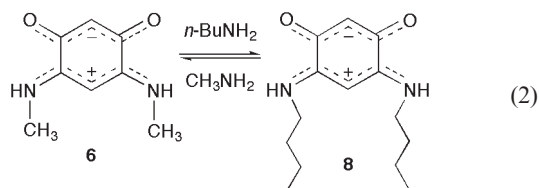
The one-pot synthesis of the new zwitterions **5–9** results from deprotonation of **2**·2HCl in the presence of amine, air oxidation to afford intermediate **A** (not isolated) which rearranges to **4**, followed by *in situ* reaction of the latter with excess amine. In 1883, Typke (erroneously) formulated the air oxidation product of **2** as C₆H₂(OH)₂(NH)₂,⁹ and after Kehrmann and Betsch¹⁰ also noted its violet-brown colour, its structure was then suggested in 1956 to correspond to **A**.¹¹ Consequently, **2** has since been considered to be an air-sensitive product that prefers to sacrifice its aromatic character in favor of a quinonoid structure. However, we



Scheme 1 One-pot synthesis of the zwitterions. **5** R = CH₂CH₂OH; **6** R = CH₃; **7** R = CH(CH₃)CH₂CH₃; **8** R = (CH₂)₃CH₃; **9** R = CH₂CH₂N(CH₃)₂.

now show that formulation of the latter as **A** is incorrect since this is only an intermediate that immediately rearranges by proton transfer to afford **4**, the parent member of this zwitterion family. Its ^1H NMR spectrum revealed the presence of two NH_2 signals, consistent with the zwitterionic form (See ESI†).

Zwitterions **5–9** can also be obtained directly from isolated **4** in high yield, supporting its role as a reaction intermediate (Scheme 1). Interestingly, treatment of N-substituted zwitterions, such as **6**, with primary amines leads to compounds such as **8** in which the N-substituent has been exchanged [eqn. (2)]. Although nucleophilic substitution reactions can occur smoothly at quinonoid compounds,^{1b,12a,b} and biochemically relevant quinone-dependent transamination reactions have been reported,^{12c} this reversible reaction represents the first example, to the best of our knowledge, of a transamination occurring on a quinonoid ring.



Primary amines with amino groups attached to a primary or secondary carbon reacted smoothly with **4**, or any derivative of type **1**, to give *i.a.* **7**, in which the amino group is attached to a secondary carbon, a compound that was not accessible by the previous synthetic method.^{3–5} For steric reasons, the reaction with secondary carbon-substituted amines requires longer reaction times.

This new efficient synthesis allows the preparation of quinoneimine zwitterions with interesting functionalities for supramolecular chemistry. An X-ray diffraction study of **5** confirmed its zwitterionic structure (*i.e.* fully delocalized π system) (Fig. 1) and showed that the two acidic hydroxyl protons are involved in hydrogen bonding interactions (Fig. 2).‡

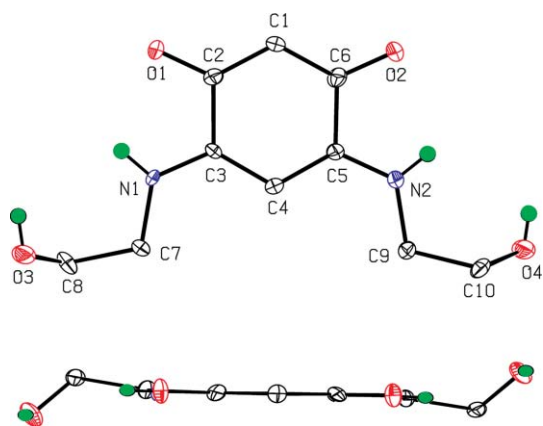


Fig. 1 Top and side views of the structure of **5** in the crystal. Thermal ellipsoids are drawn at the 50% probability level. Selected bond distances (Å) and angles (°): O(1)–C(2) 1.258(5), C(1)–C(2) 1.398(5), C(1)–C(6) 1.392(5), C(6)–O(2) 1.256(5), N(1)–C(3) 1.315(5), C(3)–C(4) 1.396(5), C(4)–C(5) 1.392(5), C(5)–N(2) 1.317(5), C(2)–C(3) 1.519(5), C(5)–C(6) 1.517(5); O(1)–C(2)–C(1) 125.3(4), O(1)–C(2)–C(3) 116.2(3), N(1)–C(3)–C(4) 124.5(3), N(1)–C(3)–C(2) 114.3(3), C(2)–C(1)–C(6) 121.7(4), C(3)–C(4)–C(5) 118.6(4).

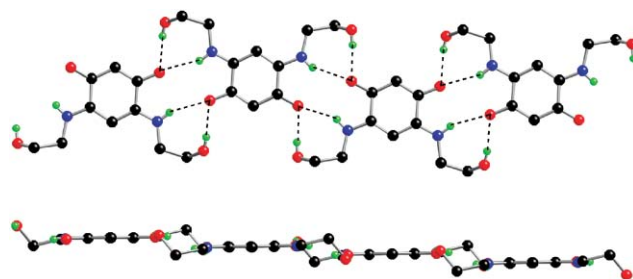
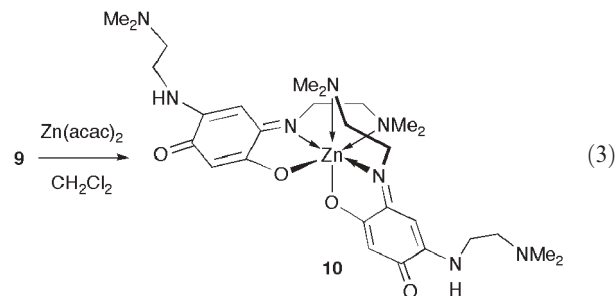


Fig. 2 Crystalmaker top and side views of the supramolecular array generated by **5** in the solid state.§ Colour coding: nitrogen, blue; oxygen, red; hydrogen, green.

Therefore, in contrast to **1** ($R = t\text{-Bu}$) which formed a head-to-tail but zig-zag arrangement in the solid state, zwitterion **5** forms a head-to-tail and coplanar supramolecular network.

Furthermore, zwitterionic **9** with a pendant coordinating “arm” was reacted with $\text{Zn}(\text{acac})_2$ in dichloromethane solution at room temperature, to afford complex **10** [eqn. (3)], which was fully characterized, including by X-ray diffraction (Fig. 3).‡‡



Coordination of the pendant amino group leads to a hexacoordinated zinc centre. Examination of the bond distances

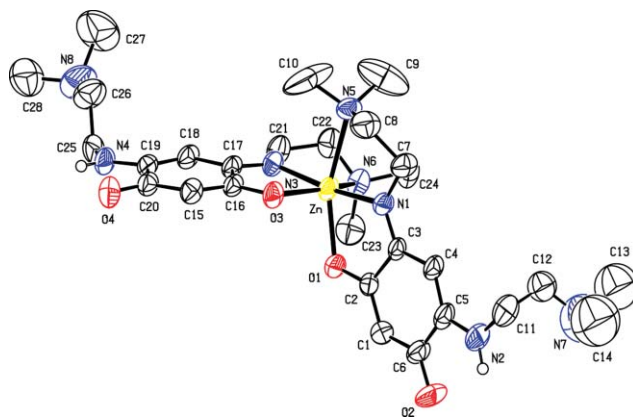


Fig. 3 ORTEP view of the structure of **10** in the crystal. Thermal ellipsoids are drawn at the 50% probability level. Selected bond distances (Å) and angles (°): Zn–N(1) 2.037(4), Zn–O(1) 2.134(4), Zn–N(5) 2.442(5), O(1)–C(2) 1.270(6), C(1)–C(2) 1.384(7), C(2)–C(3) 1.520(7), N(1)–C(3) 1.292(6), C(3)–C(4) 1.415(6), C(6)–O(2) 1.240(7), C(1)–C(6) 1.406(8), C(5)–C(6) 1.521(9), C(5)–N(2) 1.324(7), C(4)–C(5) 1.368(8); N(1)–Zn–N(3) 171.6(2), N(3)–Zn–O(3) 78.0(2), N(1)–Zn–O(3) 99.4(2), N(3)–Zn–O(1) 110.3(2), N(1)–Zn–O(1) 77.7(2), O(1)–Zn–O(3) 93.0(2), N(3)–Zn–N(6) 77.4(2), N(1)–Zn–N(6) 106.3(2), O(3)–Zn–N(6) 153.61(15), O(1)–Zn–N(6) 86.7(2), N(3)–Zn–N(5) 95.6(2), N(1)–Zn–N(5) 76.3(2), O(3)–Zn–N(5) 89.7(2), O(1)–Zn–N(5) 154.0(2), N(5)–Zn–N(6) 102.1(2).

within the quinoneimine core reveals an alternation of single and double bonds, which is consistent with localized π systems. The Zn–O(1) and Zn–N(1) distances of 2.129(3) and 2.035(4) Å, respectively, are in the expected range.¹³

The nature and geometry of the coordination sphere of Zn(II) complexes in the presence of multifunctional ligands, is currently attracting considerable attention in bioinorganic chemistry and homogeneous catalysis.¹⁴

In conclusion, we have disclosed a new and very efficient synthesis of various functional N-substituted, $6\pi + 6\pi$ electron zwitterionic benzoquinonemonoimines involving the first examples of transamination reactions on a quinonoid system. This one-pot preparation is carried out in water and allows access to new zwitterions not previously accessible. The possibility to fine-tune their solubility is important for future applications,⁸ and the introduction of new functionalities on the zwitterionic skeleton opens new possibilities in coordination and supramolecular chemistry.

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Notes and references

‡ Crystal data: Red crystals of **5** were obtained from the reaction mixture containing **1** (R = *t*-Bu) and ethanolamine in MeOH. Triclinic space group $P\bar{1}$ with $a = 5.231(1)$, $b = 9.857(1)$, $c = 10.517(1)$ Å, $\alpha = 74.67(5)$, $\beta = 76.63(5)$, $\gamma = 85.42(5)^\circ$ at 173(2) K with $Z = 2$. Refinement of 2960 reflections, and 189 parameters, yielded $wR_2 = 0.2485$ for all data [2106 reflections with $I > 2\sigma(I)$]. Red crystals of **10** were obtained by slow diffusion of pentane into a THF solution. Monoclinic space group $P2_1/c$ with $a = 12.309(5)$, $b = 17.060(5)$, $c = 15.059(5)$ Å, $\beta = 96.02(5)^\circ$ at 173(2) K with $Z = 4$. Refinement of 9138 reflections, and 335 parameters, yielded $wR_2 = 0.2402$ for all data [5303 reflections with $I > 2\sigma(I)$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. CCDC 262674

and 262675. See <http://www.rsc.org/suppdata/cc/b5/b501926e/> for crystallographic data in CIF or other electronic format.

§ CrystalMaker Software, version 5.2.0, D. C. Palmer, Bicester, Oxfordshire, UK.

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