JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c01428 • Publication Date (Web): 30 Jul 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis and Basicity Studies of Quinolino[7,8-*h*]quinoline Derivatives

Gareth J. Rowlands,[a] Rebecca J. Severinsen,[a] Jenna K. Buchanan,[a] Karl J. Shaffer,[a] Heather T. Jameson,[a] Nishani Thennakoon,[a] Ivo Leito,[b] Märt Lõkov,[b] Agnes Kütt,[b] Robert Vianello,[c] Ines Despotović,[c] Nena Radić[c] and Paul G. Plieger*[a]

[a] School of Fundamental Sciences, Massey University, Private Bag 11 222, Palmerston North, New Zealand
Email: p.g.plieger@massey.ac.nz

[b] Institute of Chemistry, University of Tartu, Ravila 14a, Tartu 50411, Estonia

[c] Ruđer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia

Abstract

Quinolino[7,8-*h*]quinoline is a superbasic compound, with a pK_{aH} in acetonitrile greater than that of 1,8-bis(dimethylaminonaphthalene) (DMAN), although its synthesis and the synthesis of its derivatives can be problematic. The use of halogen derivatives 4,9-dichloroquinolino[7,8-*h*]quinoline (**16**) and 4,9-dibromoquinolino[7,8-*h*]quinoline (**17**) as precursors has granted the formation of a range of substituted quinolinoquinolines. The basicity and other properties of quinolinoquinolines can be modified by the inclusion of suitable functionalities. The experimentally obtained pK_{aH} values of quinolino[7,8-*h*]quinoline derivatives show that N^4,N^4,N^9,N^9-tetraethylquinolino[7,8-*h*]quinoline-4,9-diamine (**26**) is more superbasic than quinolino[7,8-*h*]quinoline. Computationally derived pK_{aH} values of quinolinoquinolines functionalised with dimethylamino (NMe_2), 1,1,3,3-tetramethylguanidino ($N{=}C(NMe_2)_2$) or *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphorimidic triamido ($N{=}P(NMe_2)_3$) groups are significantly greater than that of quinolino[7,8-*h*]quinoline. Overall, electron-donating functionalities are observed to increase the basicity of the quinolinoquinoline moiety, while the substitution of electron-withdrawing groups lowers

the basicity.

Introduction

The discovery of 1,8-bis(dimethylaminonaphthalene) (DMAN) **1** (Figure 1), the original Proton Sponge™,[1] ignited an intense interest in neutral organic superbases.[2-4] The close proximity of the lone pair of electrons on the proximal nitrogen atoms causes a destabilising electrostatic interaction that can be alleviated by the coordination of a proton. The neutral species display helical distortion to ameliorate the lone pair interaction while the protonated species become planar. This has led to the preparation of a wide range of analogous organic superbases comprising various nitrogen and/or phosphorus functional groups held in close proximity.[5-7] The unique chemistry of these molecules has seen them used as models for the study of a variety of theories of bonding and reactivity.[8-13]

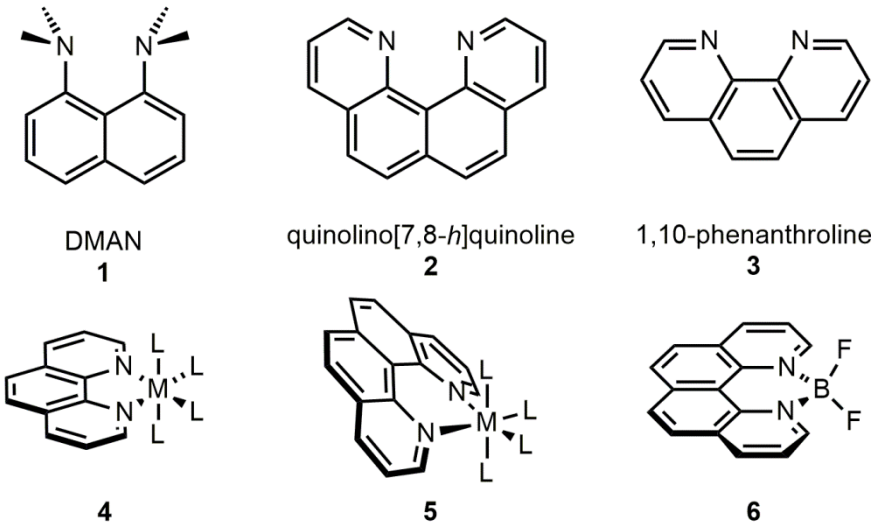


Figure 1. The structures of DMAN (**1**), quinolino[7,8-*h*]quinoline (**2**), 1,10-phenanthroline (**3**), 1,10-phenanthroline coordination (**4**), quinolino[7,8-*h*]quinoline coordination (**5**) and quinolino[7,8-*h*]quinoline coordination to boron (**6**).

One area that has seen less study is the coordination of such compounds to metals.[14-18] Only one complex of DMAN **1** itself has been reported.[19] The methyl groups cause unfavourable interactions destabilising metal complexes. It goes without saying that diamines

are the archetypal bidentate ligand and so there has been interest in using superbasic compounds as ligands in order to create reactive complexes. At first glance, the quinolinoquinoline system **2** appears to marry both concepts. The nitrogen lone pairs are forced together giving the basic properties but, by including the nitrogen in an aromatic system, the destabilising steric effects of the methyl groups have been removed. Arguably, the closest analogue to **2** is 1,10-phenanthroline **3**, a ubiquitous ligand in coordination chemistry.[20, 21] But, while there are > 45,000 hits in SciFinder for unsubstituted phenanthroline-metal complexes there are less than 20 for quinolinoquinolines (with any substitution pattern).[22]

There are undoubtedly two compelling reasons for this disparity. The first is one of access. Synthesis of quinolinoquinoline **2** and its derivatives is not simple and there has been a low supply of these compounds.[16, 23-27] The second relates to coordination environment. The five-membered ring formed on coordination of phenanthroline to a metal **4** can accommodate a wide range of metals with little distortion to either the ligand or the metal. The same cannot be said for quinolinoquinolines.[28-30] Coordination of a metal results in the formation of six-membered ring **5** that can only include small metals such as beryllium or boron **6** if there is not to be significant distortion of either the ligand or the metal.[16, 28, 30] The few examples of metal coordination to quinolinoquinolines suggests that these complexes could be useful catalyst pre-cursors.[15, 17] The high basicity appears to impart a degree of thermal stability while the out-of-plane complexation (**5**, M = Pt or Re) should make one coordination site more accessible for reaction.[15] It is clear that there needs to be more study of these compounds.

Given that there is clearly an opportunity to exploit this understudied system we wanted to develop chemistry that would allow access to a range of substituted quinolinoquinolines. This would permit us to pursue our interests in the coordination of small metals,[31] catalysis,[32,

[33] supramolecular chemistry,[34-36] and the synthesis of unusual heterocycles.[37-39]

This paper outlines the current state of syntheses of substituted quinolinoquinolines.[16, 17, 23-26] As the basicity of these compounds influences their synthesis and complexation, a study of the basicity of these compounds as determined by pK_{aH} values would be highly informative, thus an investigation of both computationally derived and experimentally obtained pK_{aH} values has been undertaken and are provided.

Results and Discussion

Naming and numbering

Quinolino[7,8-*h*]quinoline is a fused ring system, considered to be two quinoline heterocyclic ring systems fused together. While prior publications have used the prefix quino- for the quinoline ring system,[15-17, 23-26, 40, 41] we have adopted the quinolino- nomenclature due to updated IUPAC recommendations no longer listing quino- as an accepted contracted prefix.[42] The naming of this compound is based on the numbering of the parent and substituent quinoline molecules (Figure 2a).[43-45] Fusion occurs at the face, or two-atom bond, labelled *h* on the parent quinoline. The numbers 7 and 8 designate the fused atoms of the attached quinoline substituent. To number the atoms of quinolino[7,8-*h*]quinoline, the molecular structure is oriented so that the greatest number of rings are located in the upper right quandrant and the heteroatoms are assigned the lowest possible position numbers. Numbering then begins on the most counterclockwise atom of the top right ring, and proceeds in a clockwise direction around the molecule (Figure 2b). Bridgehead carbon atoms are not formally numbered, and are instead given the number of the preceding non-fused carbon atom followed by a letter (starting with "a" for an adjacent carbon atom).[43-45]

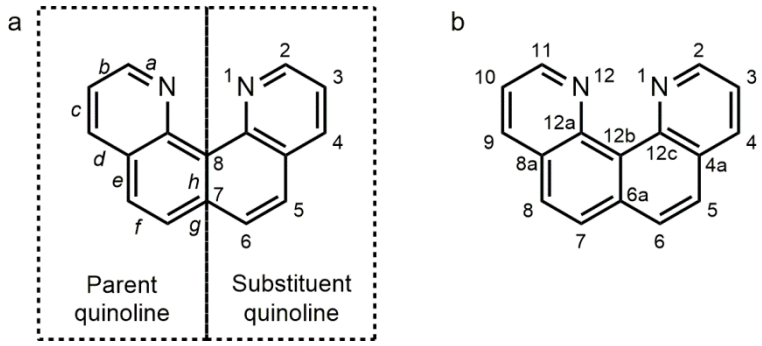
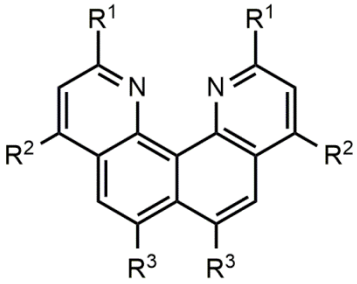


Figure 2. (a) Determination of the nomenclature of quinolino[7,8-*h*]quinoline and (b) the atom numbering scheme.

Synthesis of the quinolinoquinoline core

The synthesis of quinolinoquinolines of the type **7** is not trivial as revealed by the checkered history of these compounds. There have been a number of reported syntheses[46] that have not stood up to scrutiny.[40]



7 $R^1 = R^2 = R^3$ = general
8 $R^1 = R^3 = H$; $R^2 = Cl$
9 $R^1 = SCH_3$; $R^2 = R^3 = H$

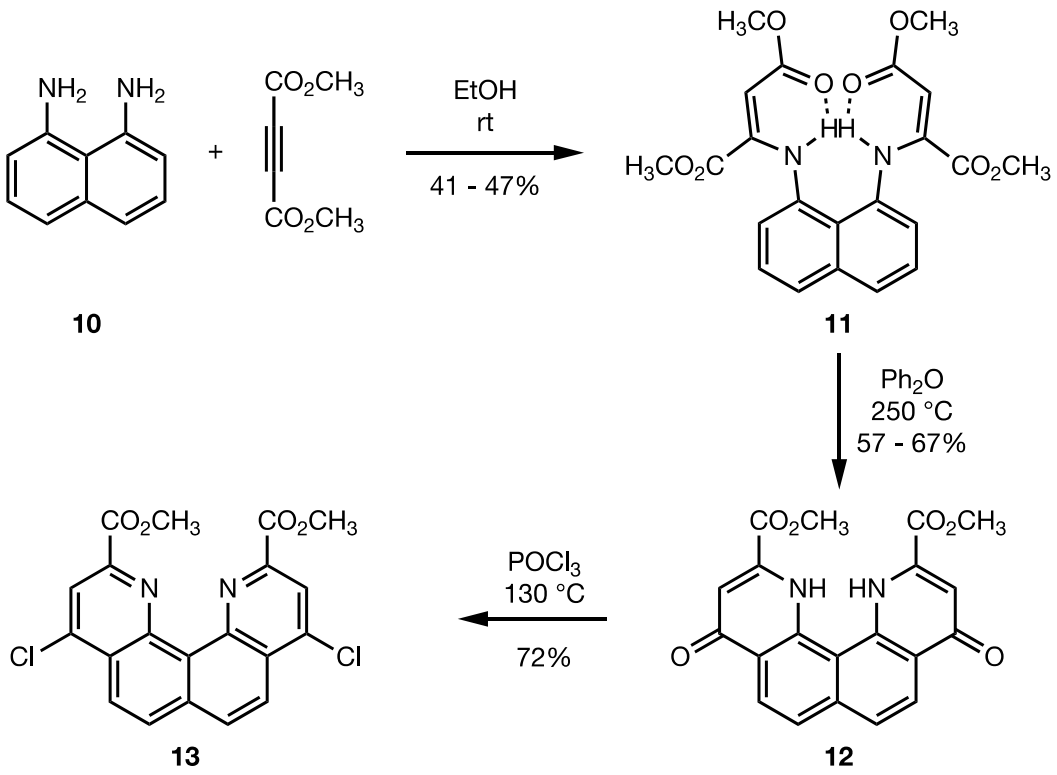
Figure 3. Structure of quinolino[7,8-*h*]quinoline derivatives.

It is widely accepted that the first synthesis of these quinolinoquinolines (**8** $R^1 = R^3 = H$; $R^2 = Cl$; and **2** $R^1 = R^2 = R^3 = H$) was by Staab and co-workers.[25, 26] The chloro derivative was first coordinated to a metal, platinum and rhenium, some 15 years later.[15] There was no mention of these compounds in the synthetic literature until a new route to 2-(methylthio)quinolines (**9** $R^1 = SCH_3$, $R^2 = R^3 = H$) was reported in 2004[47] and an

improvement on the cyclisation step of the original synthesis was detailed in 2007.[48] The former route looked attractive as the sulfide group presents a handle for modification.[49-56] Unfortunately, we have been unable to repeat this chemistry and suspect that the reaction halted after a single cyclisation and acetylation.[24]

With all this in mind, the goal of our research was to access larger quantities of quinolinoquinolines that contained a handle for subsequent functionalisation. This would enable us to study their coordination properties, tune their basicity as well as alter undesirable physical properties such as their low solubility. In order to elaborate the basic quinolinoquinoline core we required suitable functionality. The previous syntheses of such *ortho*-fused quinolines delivers ester groups at the 2,11 positions and ketones at the 4,9 positions (**12**; Scheme 1). This seemed ideal for our purposes.

Synthesis of *ortho*-fused quinoline **12** was achieved following the original Honda procedure (Scheme 1).[41] Mixing 1,8-diaminonapthalene **10** with two equivalents of dimethyl acetylenedicarboxylate in ethanol furnishes the difumarate **11** as a yellow precipitate that, after a simple wash, can be used in the cyclisation step. Addition of **11** to biphenyl ether at 250 °C followed by stirring for 20 minutes resulted in the expected product of aromatic electrophilic substitution. Again, purification was simplified by the relative insolubility of the product, filtration and washing give the product with sufficient purity to obtain microanalytical data and ^{1}H NMR in deuterated TFA.

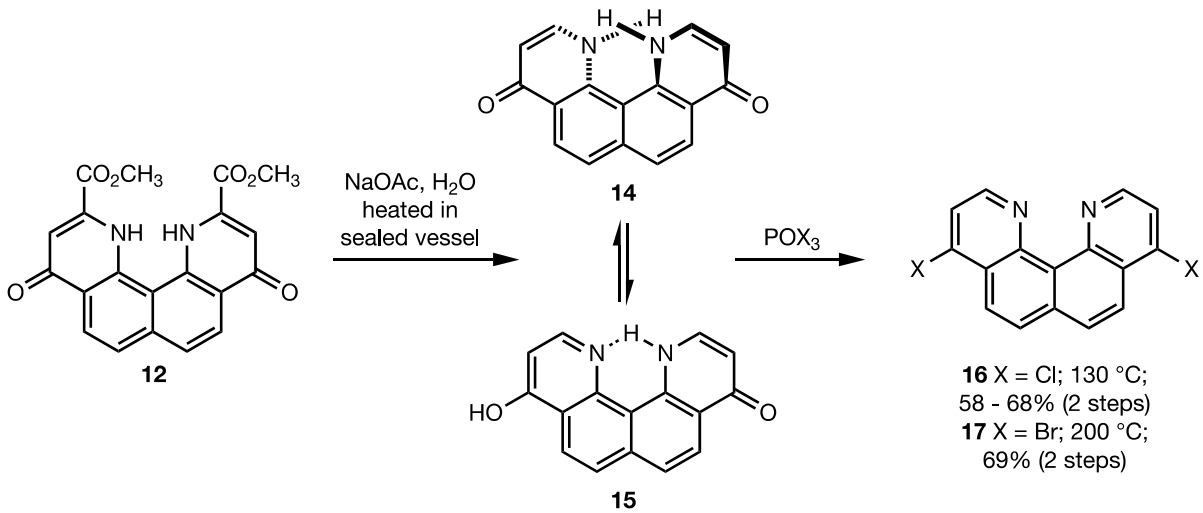


Scheme 1. Synthesis of the chloroquinoline **13**.

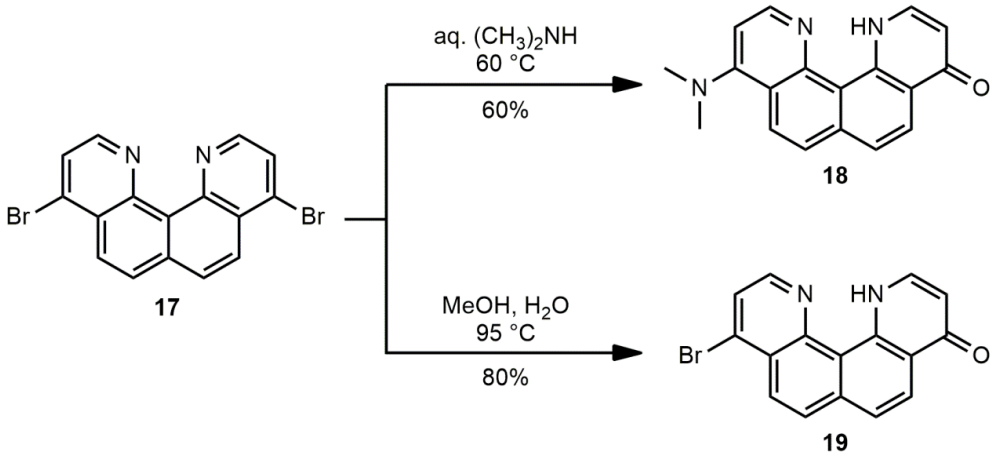
Functionalisation of the quinolinoquinoline core

Functionalisation of the pyridinone-like tetracycle **12** was problematic due to its poor solubility. Two transformations have proven high yielding. The first was aromatisation/dehydration by treatment with phosphorus oxychloride to give the chloroquinoline **13**. A protonated version of this compound was fully characterised including X-ray crystallographic data.[24] It shows the expected planar arrangement with an internal hydrogen bond between the ester carbonyl and the proton. So far, all attempts to derivatise this molecule by either reducing the esters or substituting the chlorine atoms have met with failure. Even so, to the best of our knowledge this remains the only 2,11-disubstituted quinolinoquinoline that is capable of more than bidentate coordination, and as such shows potential for future study.

The second transformation involves hydrolysis and decarboxylation to give the *ortho*-fused quinolinone (Scheme 2). When we started this research, this step represented the bottleneck for the synthesis of quinolinoquinolines: the reported procedure involved hydrolysis followed by a high temperature (370 °C) and low-pressure decarboxylation (10^{-5} torr) performed in a sublimation apparatus. We have developed a two-step, 'one-pot' reaction based on chemistry by Strauss and Trainor[57] that permits this transformation to be achieved far more readily. Heating a mixture of diester **12** and sodium acetate in water to 250 °C for 1 hour in a microwave reactor gives **15** of sufficient purity that it can be purified after the subsequent aromatisation reaction (Scheme 2).[16] While reaction in a microwave is convenient, we found it easier to scale the reaction by performing it under conventional heating in a Teflon-lined stainless steel sealed vessel over a period of 12 - 16 hours.[16] Chlorination with phosphorus oxychloride delivered the *ortho*-fused quinolinoquinoline **16** in good yield for the two steps. Alternatively, the bromide **17** could be formed by treatment with phosphorus oxybromide. This compound is more reactive than the chloride. Initial attempts to hydrolyse **17** in aqueous dimethylamine gave the substituted and hydrolysed dimethylamino quinolinone **18** (Scheme 3). In the absence of dimethylamine, **17** readily undergoes a single hydrolysis to give the non-symmetric quinolinone **19**. Calculations show that keto-**19** as drawn is 16.4 kcal mol^{-1} more stable than enol-**19**.



Scheme 2. Synthesis of halogen derivatives **16** and **17**.



Scheme 3. Synthesis of quinolinones **18** and **19**.

The previous synthesis of **16** suggested that the intermediate is the *ortho*-fused quinolinone **14**.[25] While we have not fully characterised this molecule, infrared spectroscopy would suggest that the tautomer, **15**, predominates.[16] In addition, our calculations at the B3LYP/6–31+G(d,p) level show that **15** is by 12.0 kcal mol^{-1} more stable than **14**, and by 17.6 kcal mol^{-1} than a potential 4,9-dihydroxy tautomer, thus confirming the experiments. This tautomer maximises aromaticity and minimises structural distortions. The *ortho*-fused quinolinone forces two hydrogen atoms into close proximity and arrangement that can only be accommodated if the molecule adopts a helical twist. Based on computational modelling, the torsional angle for this helical twist in **14** is 22.0°. Tautomerisation leads to a planar structure and would be in keeping with subsequent results.

Interestingly, Staab and co-workers[26] reported that the dechlorinated derivative **2** is planar in the solid state. This is unusual for molecules with a 'proton sponge'-like structure, where the lone pair interactions distort the core to give a helical twist to the molecule. After inspection of the data, it is almost certain that hydrogen bonding between **2** and a bridging water molecule alleviates unfavourable interactions. X-ray crystallographic analysis of crystals of **16** grown under anhydrous conditions reveal this molecule to have the expected

distortion in the solid state of 20.02(9)° (Figure 4a).[16] Protonation of **16** stops the unfavourable lone pair interactions and gives a planar species (Figure 4b). This is confirmed by our computational analysis, which shows that in **16** the helical torsional twist is 21.1°, indicating a non-planarity. Upon protonation, in **16**H^+ the same dihedral angle assumes 0.0°, thus clearly indicating the planarisation.

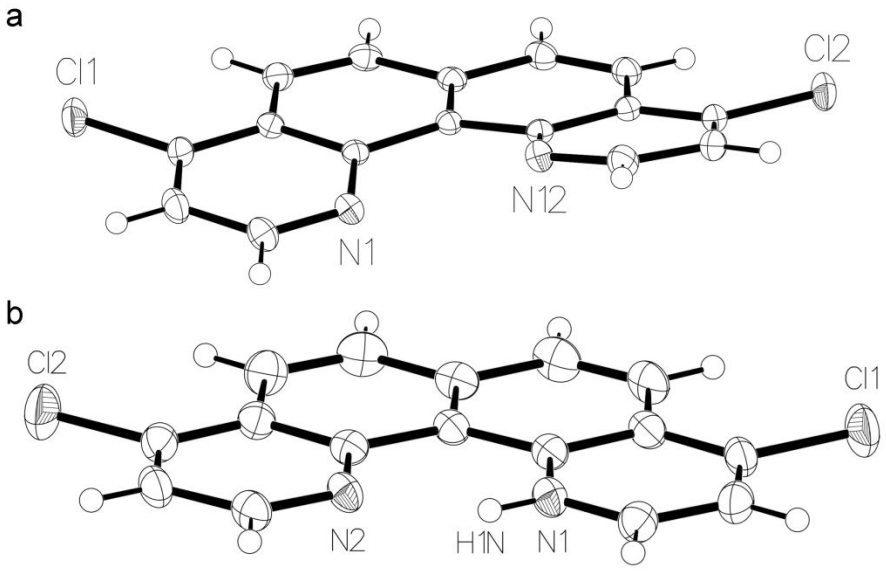
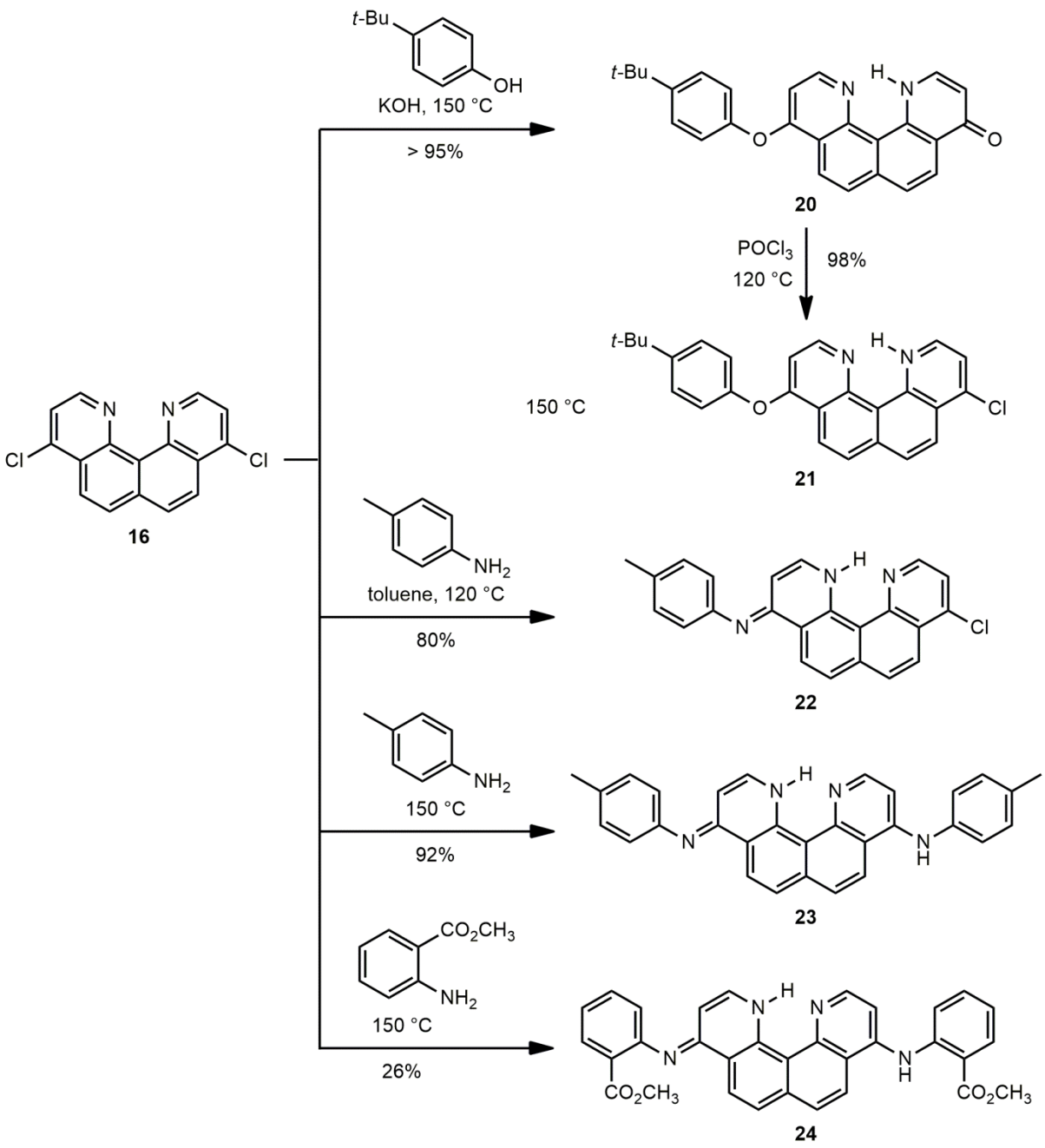


Figure 4. X-ray crystal structures of the neutral (a) and protonated (b) forms of **16**. Chloroform solvent molecules for (a) and the tetrafluoroborate counter ion for (b) have been removed for clarity, ellipsoids are drawn at the 50% probability level.[16]

Nucleophilic substitution of halogen appended derivatives

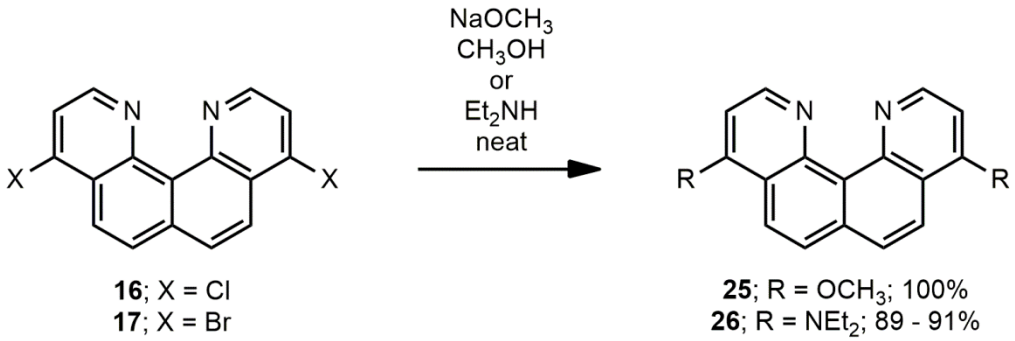
We first investigated the substitution of the chlorides in the hope that this would improve the limited solubility of **16** as well as allowing the basicity to be tuned. Indeed, our calculations shows that the gas-phase proton affinity of the parent **2** is reduced from 255.4 to 251.0 kcal mol^{-1} when two chlorine atoms are introduced as in **16**. Yet, when the latter substituted by the electron-donating group, such as dimethylamino moiety, the resulting proton affinity increases to 269.0 kcal mol^{-1} (see later). Formation of aromatic ethers and

amines was attempted used the methodology of Schmittel.[58] Reaction of **16** with 4-*tert*-butylphenol and KOH furnishes the non-symmetric monoether **20** in which one of the chlorides has been hydrolysed to give the quinolinone tautomer (Scheme 4). Subsequent reaction with phosphorus oxychloride yields the monochloride **21**.[24] The more nucleophilic toluidine does not require external base and furnishes either the mono-imine **22** or the product of double displacement **23** depending on whether the reaction is performed in toluene or a melt formed from neat toluidine at 150 °C. A similar reaction delivered the highly fluorescent ester derivative **24**.[24] In each case, addition results in the formation of a tautomer in which the disfavoured lone pair interactions are ameliorated by protonation.



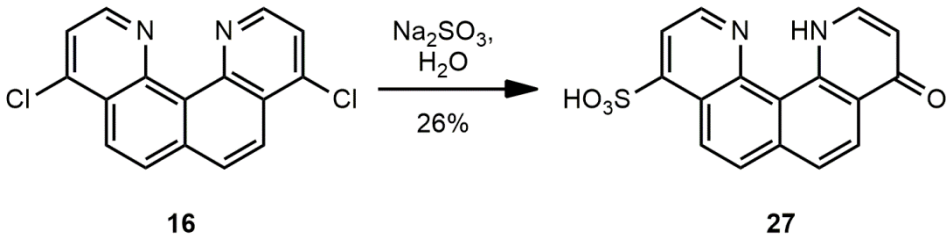
Scheme 4. Nucleophilic substitution of **16** with oxygen and nitrogen donors.

Similar chemistry permits the synthesis of alkyl ethers and amines as well. With a strong nucleophile, such as sodium methoxide, the dichloro-derivative **16** was used but for the less nucleophilic amine the more reactive dibromide **17** was required (Scheme 5).



Scheme 5. Synthesis of **25** and **26** by nucleophilic substitution.

We were also interested in making a water soluble quinolinoquinoline by substituting the chloride groups of **16** with sulfonic acid moieties via reaction with sodium sulfite. While the mass spectrum of the reaction mixture showed some di-substitution of the chloride groups, the only stable product formed over a range of reaction conditions was the monosulfonate **27** (Scheme 6). NMR analysis confirmed the formation of **27** rather than the phenol tautomer. This was supported by our calculations, which showed **27** is 15.3 kcal mol^{-1} more stable than the phenol tautomer.

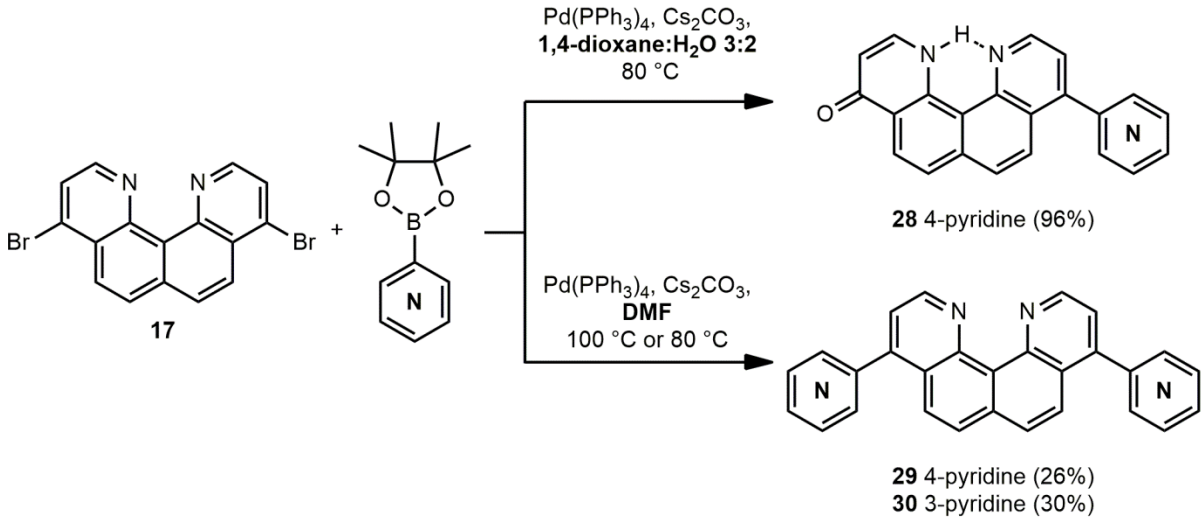


Scheme 6. Synthesis of the monosulfonate quinolinone **27**.

Palladium-catalyzed cross-coupling reactions

Formation of the dibromide **17** opened the door for palladium-catalyzed cross-coupling reactions as a route to functionalise the quinolinoquinoline core. Our initial attempts utilised 4-pyridineboronic acid pinacol ester as the coupling partner. Under typical Suzuki-Miyaura reaction conditions using $Pd(PPh_3)_4$ as the pre-catalyst, Cs_2CO_3 as base and a mixture of 1,4-

dioxane and water as solvent, the monopyridine derivative **28** could be isolated in 96% yield (Scheme 7). X-ray crystallographic analysis of **28** confirms the quinolinone tautomer is formed (Figure S1). The water was included in the mistaken belief that it would increase the rate of reaction either by affecting hydrolysis of the boron ester, or promoting formation of either the boronate or oxo-palladium species.[59] With hindsight, it is clear that the addition of water leads to hydrolysis of one bromide to form the hydrogen bond-stabilised quinolinone. The second, activated, bromide then participates in the cross-coupling reaction.



Scheme 7. Synthesis of 3-pyridine and 4-pyridine functionalised quinolinoquinolines via palladium-catalyzed cross-coupling reactions.

Performing the reaction under anhydrous conditions with dry DMF as solvent led to the desired dipyridine **29**. For the 4-pyridine derivative, moderate conversion was observed (~ 60%) along with formation of a small quantity of the mono-pyridine derivative **28**. Purification was problematic with the only success being achieved with fractional crystallisation, which gave a disappointing 26% of the pure material.

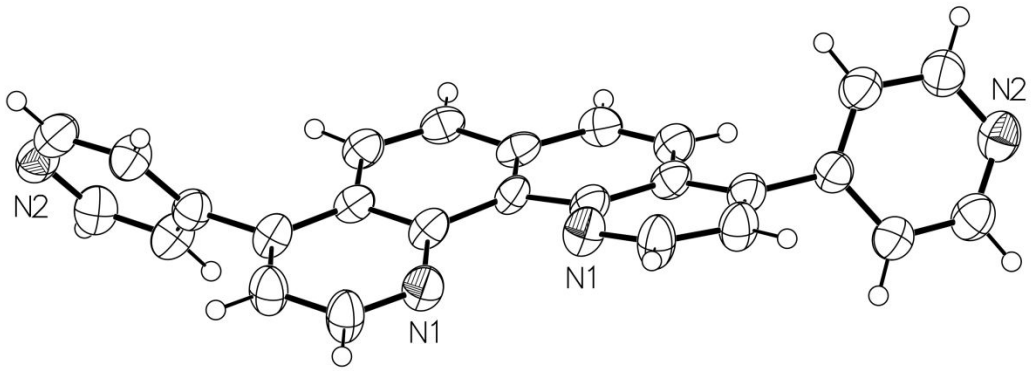
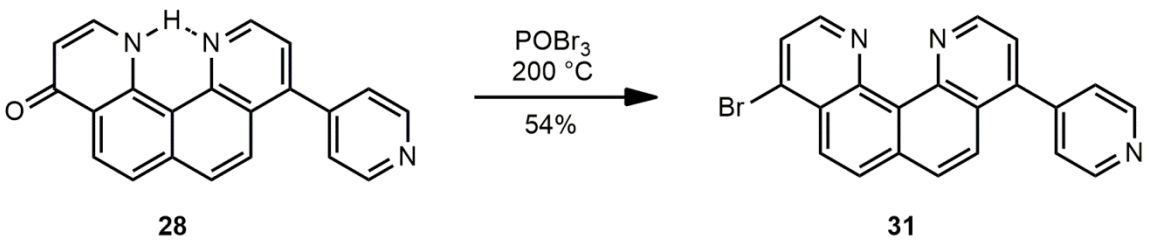


Figure 5. X-ray crystal structure of **29**; ellipsoids are drawn at the 50% probability level.

The structure of the compound **29** was confirmed by X-ray crystallography (Figure 5). This shows the expected helical twist in the quinolinoquinoline core, as the nitrogen lone pairs minimise interaction. The helical torsional twist is significantly greater at 24.19(12)° than that observed in the dichloro derivative **16** (20.02(9)°). This is in excellent agreement with the calculated helical torsional twist of 23.3°. The pyridyl side groups are each twisted at 63.29° angles to the mean central plane and sit almost perpendicularly with respect to each other (83.01°). The divergent angle of these pyridine groups will prevent coordination to the same metal ion.

Similarly, it is possible to prepare the di-3-pyridine derivative **30** utilising the anhydrous coupling conditions. Fractional crystallisation results in a yield of 30%.

The monopyridine quinolinone **28** can be primed for a second coupling reaction by bromination. This would allow the preparation of non-symmetric quinolinoquinolines. Simply re-subjecting this compound to the standard bromination conditions gave the desired quinolinoquinoline **31** in 54% yield (Scheme 8).

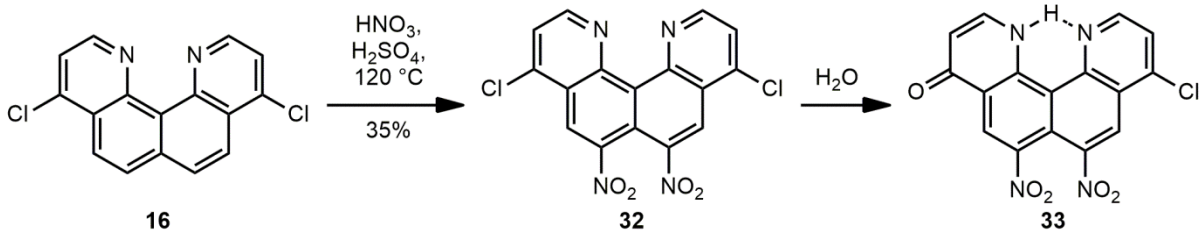


28 **31**

Scheme 8. Synthesis of the non-symmetric quinolinoquinoline **31**.

Electrophilic aromatic substitution reactions

Having investigated substitution at the 2,11- and 4,9-positions, we were also interested in functionalisation of the 6,7-positions of the core. One of the simplest methods is electrophilic aromatic substitutions such as nitration. Such chemistry would install a nitrogen atom into the molecule that might permit further functionalisation at a later stage. Addition of dichloride **16** to a pre-heated mixture of fuming nitric acid and concentrated sulfuric acid for just 2 minutes gave the dinitro compound **32** in 35% yield (Scheme 9). All data suggests formation of this isomer but, not unexpectedly, this derivative shows limited solubility and characterisation has been challenging. Mass spectroscopy confirms this composition.



16 **32** **33**

Scheme 9. Synthesis of the dinitro quinolinoquinoline **32** and subsequent hydrolysis.

Eventually, we were able to grow crystals suitable for X-ray crystallographic analysis (Figure S3). These indicated hydrolysis of one of the chloro substituents occurred during recrystallisation. As expected, once hydrolysis occurs, the planar hydrogen bond stabilised quinolinone tautomer **33** is formed. Due to this compound being the unsought hydrolysis

product, no further characterisation was attempted.

The work above presents the most comprehensive study of *ortho*-fused quinoline proton sponge analogues to date. We have shown that a functionalised core can be readily accessed in synthetically useful quantities. The halogenated derivatives, **16** and **17**, act as good precursors to a range of new compounds. This will permit the basicity of this system to be fine-tuned as well as the development of new and useful materials.

Throughout the synthetic studies the propensity for these compounds to undergo hydrolysis and form a hydrogen bond-stabilised *ortho*-fused quinoline quinolinone system has plagued efficient transformations. We suspect that the basic nature of these proton sponge analogues leads to protonation of the nitrogen and activation of one of the halogen atoms. To gain more insight into the basicity of this core, experimental and computational studies were undertaken on a number of the derivatives.

Experimental basicity studies

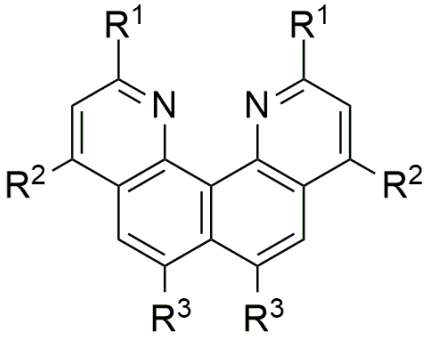
The methodology and experimental set up for the quinolinoquinoline derivatives in acetonitrile was essentially the same as in previous publications.[60, 61,] The terminology pK_{aH} has been used to express the basicity of each base, rather than pK_a, to clearly express that it refers to the protonation of a base (or deprotonation of the protonated base).[2] The determined pK_{aH} values for quinolino[7,8-*h*]quinoline and its derivatives are given in Table 1. A superbase has occasionally been defined as a base with pK_{aH} value of the conjugate acid greater than that of the proton sponge DMAN.[2] The pK_{aH} of DMAN in acetonitrile is 18.63.[62] Based on this definition, two of the compounds for which pK_{aH} was measured had values consistent with that of a superbase. The assigned pK_{aH} for quinolino[7,8-*h*]quinoline was 19.60,[62] greater than that of DMAN in acetonitrile. The diamine derivative **26** had a higher pK_{aH} of 23.97, suggesting an even greater ability to act as a superbase. The increased basicity

of **26** compared to quinolino[7,8-*h*]quinoline is likely due to the activating diethylamino groups which increase electron delocalisation and help to stabilise the positive charge of the conjugate acid.

Compounds **16** and **17** both had experimentally determined pK_{aH} values slightly less than that of DMAN, while the pK_{aH} values of **13**, **15** and **20** were significantly lower. Therefore these five quinolino[7,8-*h*]quinoline derivatives cannot be classified as superbases. The quinolinoquinoline derivatives **13**, **16** and **17** contain deactivating groups which would destabilise the conjugate acid by withdrawing electron density from the aromatic system. The $–CO_2CH_3$ group in **13** is a stronger deactivating group than the halogens in **16** and **17**, accounting for its lower basicity. The reduced basicity in **15** and **20** can be attributed to the increased stability of the neutral base due to prototropic tautomerism, involving the proton transfer from an –OH group to the pyridine nitrogen.

We also investigated the effect of the angle of the helical torsional twist on the pK_{aH} of quinolino[7,8-*h*]quinoline derivatives. Computational analysis reveals the most basic derivative, **26**, has a change in torsional angle from 29.1° to 5.0° upon protonation. However, **13** has a similar calculated helical torsional twist is 28.4° in the neutral base and 6.0° in the protonated form and yet has a significantly lower basicity. Both **15** and **20** are planar structures due to the prototropic tautomerisation, and yet they record higher pK_{aH} values in comparison to **13**. The neutral bases of **2**, **16** and **17** have torsional angles of 17.3°, 21.1° and 19.0°, which do not correlate with the respective pK_{aH} values. Looking at all factors, it appears the size of the helical torsional twist of the neutral base does not affect the basicity of quinolino[7,8-*h*]quinoline derivatives. Instead the basicity is heavily dependent on the presence of electron withdrawing or electron donating groups.

Table 1. Experimentally determined pK_{aH} in acetonitrile and calculated proton affinities (PA), gas-phase basicities (GB) and pK_{aH} in acetonitrile for quinolinoquinoline derivatives.



Structure	Functionality	Experimental	Calculated		
		pK_{aH}	PA (kcal mol^{-1})	GB (kcal mol^{-1})	pK_{aH}
2	$R^1 = R^2 = R^3 = H$	19.60	255.4	246.8	19.6
13	$R^1 = CO_2CH_3$, R^2 = Cl, $R^3 = H$	9.24	248.8	240.8	9.9
15[a]	$R^1 = R^3 = H$, R^2 = OH	12.21	242.9	235.0	12.4
16	$R^1 = R^3 = H$, R^2 = Cl	17.64	251.0	243.0	17.3
17	$R^1 = R^3 = H$, R^2 = Br	17.58	250.8	242.2	17.2
20[b]	$R^1 = R^3 = H$, R^2-1 = 4-*t*Bu-PhO, R^2-2 = OH	12.10	245.4	237.2	12.5
26	$R^1 = R^3 = H$, R^2 = NEt_2	23.97	269.5	260.8	23.0
32	$R^1 = H$, $R^2 = Cl$, R^3 = NO_2		236.4	228.3	12.1
I	$R^1 = NMe_2$, R^2 = $R^3 = H$		259.8	251.6	20.3
II	$R^1 = N{=}C(NMe_2)_2$,		281.4	272.6	29.9

	$R^2 = R^3 = H$			
III	$R^1 = N{=}P(NMe_2)_3$, $R^2 = R^3 = H$	286.6	280.7	31.4
IV	$R^1 = R^3 = H$, $R^2 = NMe_2$	269.0	261.4	23.6
V	$R^1 = R^3 = H$, $R^2 = N{=}C(NMe_2)_2$	279.3	273.3	26.0
VI	$R^1 = R^3 = H$, $R^2 = N{=}P(NMe_2)_3$	290.6	283.2	29.6
VII	$R^1 = R^2 = H$, $R^3 = NMe_2$	262.8	254.9	20.8
VIII	$R^1 = R^2 = H$, $R^3 = N{=}C(NMe_2)_2$	271.7	264.9	22.5
IX	$R^1 = R^2 = H$, $R^3 = N{=}P(NMe_2)_3$	275.9	269.3	23.0
X	$R^1 = R^2 = R^3 = NMe_2$	273.8	266.4	24.2
XI	$R^1 = R^2 = R^3 = N{=}C(NMe_2)_2$	298.1	290.6	33.1
XII	$R^1 = R^2 = R^3 = N{=}P(NMe_2)_3$	303.3	295.8	35.5

[a] Neutral base exists as the quinolinone tautomer **15** in Scheme 2.

[b] Neutral base exists as the quinolinone tautomer **19** in Scheme 4.

Computational basicity studies

Next, we investigated the basicities of other quinolino[7,8-*h*]quinoline derivatives yet to

be synthesised and compared those with some of the systems reported here. By functionalising **2** with electron donating dimethylamino (NMe_2), 1,1,3,3-tetramethylguanidino ($N{=}C(NMe_2)_2$), or *N*,*N*,*N*′,*N*′,*N*″,N″-hexamethylphosphorimidic triamido ($N{=}P(NMe_2)_3$) groups we hoped to further improve the basicity of the quinolino[7,8-*h*]quinoline motif. Structures with these functionalities at the X, Y and/or Z positions were modelled computationally and their gas-phase proton affinities (PAs), gas-phase basicities (GBs) and pK_{aH} in acetonitrile calculated (Table 1).

Monoprotonation of the parent **2** to give the cation [**2**-H]$^+$ has an associated PA of 255.4 kcal mol^{-1}. This makes it a stronger base than DMAN (PA = 245.8 kcal mol^{-1}),[60] and justifies the choice of the quinolino[7,8-h]quinoline core in the design of highly potent organic superbases. In the conjugate acid, the attached proton is placed on one of the nitrogen atoms with d(N–H) = 1.056 Å, and hydrogen-bonded to another pyridine nitrogen with d(N·····N) = 2.613 Å, d(NH·····N) = 1.704 Å and the N–H·····N angle of 141.2°. Such asymmetry of the protonation fragment is seen in all other studied bases, and is in line with earlier reports on similar systems.[13, 63] However, calculations at the B3LYP/6–31+G(d,p) level show that the transition state for the proton transfer from one pyridine nitrogen to another lies only 0.7 kcal mol^{-1} above the asymmetric [**2**-H]$^+$, which features a single negative frequency of 1163*i* cm^{-1} corresponding to the N–H·····N ↔ N·····H–N vibration, resulting in a symmetrical structure with d(N·····N) = 2.477 Å, both d(NH·····N) = 1.286 Å and the N–H·····N angle of 149.0°. Such a small barrier allows a spontaneous proton shuttle in solution and likely in the solid state, as it was observed earlier in related derivatives.[64, 65] Each of the quinolino[7,8-*h*]quinoline derivatives had greater PAs and GBs than **2**, which can be attributed to the added functionalities acting as activating groups, donating electron density to the aromatic system and further stabilising the conjugate acid formed. Interestingly, both halogeno derivatives **16** and **17** are stronger bases than their hydroxyl analogue **15**. This is brought about as a result of

the prototropic tautomerism in the latter, involving the proton transfer from one of the –OH groups to the pyridine nitrogen, which stabilised the neutral base and reduces the resulting basicity. This effect is equally seen in both the gas-phase (around 8 kcal mol^{-1}) and acetonitrile solution (around 5 pK_{aH} units). Nevertheless, attachment of further electron-withdrawing substituents, as in **32**, significantly reduces the basicity, as two nitro groups at positions 6 and 7 lower both the proton affinity and pK_{aH} value by 14.6 kcal mol^{-1} and 5.2 units, respectively. Substitution of one of the –OH groups with the 4-*t*Bu-PhO substituent, as in **20**, reduces the magnitude of this effect and improves the basicity in the gas-phase, yet without a significant effect in the solution. Disubstituted derivatives confirm an already observed trend in which systems with the phosphazeno groups surpass the basicity of those with guanidino and dimethylamino moieties,[7] being fully in line with the electron-donating ability of those substituents. This is evident in all of the corresponding triads, namely **I**–**III**, **IV**–**VI** and **VII**–**IX**. Interestingly, the largest basicity-amplifying effect is observed when substituents are placed at the *para*-position to the quinolinoquinoline nitrogen. We attribute this to the fact that at the *ortho*-position, despite being closer to the protonation centre, the attached groups cause steric interference which reduces their optimal effect. When placed at positions 6 and 7, the effect is diminished due to the further distance from the protonation site. Accordingly, the greatest proton affinity of 290.6 kcal mol^{-1} was calculated for **I**, which also had the greatest gas-phase basicity and pK_{aH} of disubstituted compounds. In hexasubstituted systems, the phosphazene derivative **XII** again dominates with the gas-phase proton affinity exceeding the hyperbasicity limit of 300 kcal mol^{-1},[66] reaching PA = 303.3 kcal mol^{-1} and pK_{aH} = 35.5, being the strongest superbase investigated here.

The calculated pK_{aH} for quinolino[7,8-*h*]quinoline (**2**) (19.6) is in excellent agreement with the literature value of 19.60,[62] which holds for all other systems where this comparison is available (Table 1). This confirms the validity of the employed computational methodology

and renders other results reliable as well.

Conclusions

This work provides an as current comprehensive study of the synthesis of quinolino[7,8-*h*]quinoline and its derivatives. The functionalised core can be synthesised in appreciable quantities, with the halogen derivatives **16** and **17** acting as precursors for a range of new compounds. The tendency for quinolinoquinoline compounds to hydrolyse and form hydrogen bond stabilised quinolinone tautomers has been problematic throughout the synthetic studies. A number of new quinolino[7,8-*h*]quinoline derivatives have been presented, which has allowed for the investigation into the basicity of these compounds.

Quinolino[7,8-*h*]quinoline is already appreciably basic, surpassing both the gas-phase and acetonitrile solution basicities of DMAN, which makes it a superbasic system in both phases. The synthesised quinolinoquinoline **26** presented an even greater basicity than quinolino[7,8-*h*]quinoline, with the electron-donating diethylamino groups thought to destabilise the conjugate acid. Computational studies show that careful substitution of the quinolino[7,8-*h*]quinoline skeleton allows fine tuning of the resulting basicity, with electron-accepting groups reducing the basicity parameters. Electron-donating moieties increase the resulting basicity and this effect is highest when these are introduced at positions 4 and 9, *para* to the quinolinoquinoline nitrogen. Several modelled compounds had calculated pK_{aH} values greater than any experimentally determined for a quinolino[7,8-*h*]quinoline derivative, showing the potential for increased superbasicity of these compounds.

Experimental section

General Procedures: Unless otherwise stated, all reagents and solvents were purchased

from commercial sources and used without purification. The heat source for all syntheses was a temperature-controlled oil bath, with paraffin oil for temperatures less than 100 °C and silicone oil for temperatures greater than 100 °C. NMR spectra were collected on Bruker Avance 500 and 700 MHz spectrometers. All chemical shifts are reported relative to residual solvent (^{1}H, ^{13}C). Microanalyses were performed at the Campbell Microanalytical Laboratory at the University of Otago. High resolution mass spectra were recorded on either a micrOTOF-Q mass spectrometer, operating at a nominal voltage of 3500 V, or a Thermo Scientific Q-Exactive Focus Hybrid Quadrupole-Orbitrap mass spectrometer. IR and UV-Vis spectra were recorded with a Nicolet 5700 FT-IR and a UV-1800 Shimadzu spectrophotometer respectively.

Synthesis of 4,9-dibromoquinolino[7,8-*h*]quinoline (17): Phosphorus oxybromide (2.97 g, 10.4 mmol) was added to **14** (0.520 g, 2.08 mmol) and the reaction was stirred at 200 °C for 30 min under an atmosphere of Ar. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and MeOH (20 mL) and basified with 6M KOH (20 mL) in water (200 mL). A small portion of decolourising carbon was added and the organic layer was filtered and dried with $MgSO_4$ to give **17** (0.533 g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.18 (brd, *J* = 4.7, 2H), 8.51 (d, *J* = 8.9, 2H), 8.09 (d, *J* = 8.9, 2H), 7.94 (d, *J* = 4.7, 2H) ppm. $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ = 149.8, 148.2, 136.4, 134.4, 129.0, 128.8, 127.8, 126.1, 125.5 ppm. HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_9N_2{}^{79}Br{}^{81}Br$ 388.9107; Found 388.9102.

Synthesis of 9-(dimethylamino)quinolino[7,8-*h*]quinoline-4(1*H*)-one (18): Dimethylamine solution (40% aq., 15 mL) was added to **17** (57 mg, 0.148 mmol) and heated under reflux for 24 - 48 h. Water (150 mL) was added and the residue was extracted with CH_2Cl_2 (150 mL). The organic layer was washed with water (2 x 100 mL), dried with $MgSO_4$, filtered, and dried *in vacuo* to give **18** (26 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ

= 16.15 (s, 1H; N*H*), 8.68 (d, *J* = 5.4 Hz, 1H), 8.58 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.90 (dd, *J* = 6.5, 6.5 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 6.97 (d, *J* = 5.4 Hz, 1H), 6.51 (d, *J* = 6.6 Hz, 1H), 3.11 (s, 6H; C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 178.3, 158.5, 148.9, 147.2, 144.1, 140.7, 137.4, 136.2, 125.8, 125.6, 124.6, 123.1, 120.5, 117.6, 111.5, 108.1, 44.1 ppm. HRMS (ESI/Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}N_3O$ 290.1288; Found 290.1278.

Synthesis of 9-bromoquinolino[7,8-*h*]quinoline-4(1*H*)-one (19): A 2:3 MeOH:H_2O (5 mL) was added to **17** (6 mg, 0.0155 mmol) and heated under reflux for ~14 h. The solvent was removed *in vacuo* then the precipitate dissolved in a solution of 24:1 $CHCl_3$:MeOH (25 mL). The solution was washed with water (3 x 30 mL), dried with $MgSO_4$, filtered, and dried *in vacuo* to give **19** (4 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 15.49 (s, 1H; N*H*), 8.85 (d, *J* = 4.9 Hz, 1H), 8.77 (d, *J* = 8.6 Hz, 1H), 8.37 (d, *J* = 9.1 Hz, 1H), 8.08 (d, *J* = 9.1 Hz 1H), 8.01 – 7.98 (m, 2H), 7.86 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 7.3 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 178.4, 176.1, 148.3, 146.8, 146.4, 140.3, 137.8, 137.1, 130.4, 127.2, 126.5, 125.6, 123.5, 112.1, 108.1 ppm. HRMS (ESI/TOF) m/z: = $[M + H]^+$ Calcd for $C_{16}H_{10}N_2O^{81}Br$ 326.9951; Found 326.9975.

Synthesis of N^4,N^4,N^9,N^9-tetraethylquinolino[7,8-*h*]quinoline-4,9-diamine (26): Excess neat diethylamine (20 mL) was added to **17** (100 mg, 0.258 mmol) and heated under reflux for 48 – 72 h. Water (50 mL) was added and the residue was extracted with CH_2Cl_2 (100 mL). The organic layer was washed with water (3 x 100 mL), dried with $MgSO_4$, filtered and dried *in vacuo* to give **26** (86 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 19.42 (s, 1H; N*H*), 9.22 (dd, *J* = 3.0, 6.2 Hz, 2H), 8.23 (d, *J* = 9.1 Hz, 2H), 7.98 (d, *J* = 9.1 Hz, 2H), 7.30 (d, *J* = 6.2 Hz, 2H), 3.68 (q, *J* = 7.1 Hz, 8H; *C*H_2CH$_3$), 1.38 (t, *J* = 7.1 Hz, 12H; CH$_2$*C*H$_3$) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 158.6, 144.5, 144.4, 135.9, 125.6,

125.3, 119.8, 117.1, 108.9, 47.2, 12.4 ppm. HRMS (ESI/Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{24}N_4H_{29}$ 373.2387; Found 373.2385.

Synthesis of 9-oxo-9,12-dihydroquinolino[7,8-*h*]quinoline-4-sulfonic acid (27): Sodium sulfite (0.084 g, 6.667 mmol) and **16** (0.050 g, 0.167 mmol) in water (10 mL) was refluxed for 4 h. The solvent was removed and the crude reaction mixture was dissolved in DMSO and filtered then precipitated with EtOAc to give **27** (0.093 g, 26%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 15.47 (d, *J* = 4.2 Hz, 1H; N*H*), 9.20 (d, *J* = 4.6 Hz, 1H), 9.03 (d, *J* = 9.2 Hz, 1H), 8.45 (d, *J* = 8.5 Hz, 1H), 8.30 (dd, *J* = 6.7, 6.7 Hz, 1H), 8.16 (d, *J* = 9.2 Hz, 1H), 8.13 (d, *J* = 4.6 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 6.34 (d, *J* = 7.1 Hz, 1H) ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ = 176.5, 152.9, 148.2, 147.2, 139.6, 139.6, 135.8, 127.9, 127.4, 125.2, 124.4, 123.2, 123.1, 118.9, 116.7, 110.6 ppm. HRMS (ESI/TOF) m/z: $[M - H]^-$ Calcd for $C_{16}H_9N_2O_4S$ 325.0283; Found 325.0289.

Synthesis of 9-(pyridin-4-yl)quinolino[7,8-*h*]quinoline-4(1*H*)-one (28): A 1,4-dioxane : water solution (3:2, 20 mL) was added to a mixture of **17** (100 mg, 0.258 mmol), 4-pyridine boronic acid pinacol ester (211 mg, 1.03 mmol), caesium carbonate (420 mg, 1.29 mmol) and the $Pd(PPh_3)_4$ catalyst (15 mg, 0.013 mmol) and stirred at 80 °C for 16 h under an atmosphere of Ar. Water (50 mL) was added and the residue extracted with $CHCl_3$. The aqueous layer was washed with $CHCl_3$ (2 x 25 mL) and the combined organic layers were dried with $MgSO_4$, filtered and dried *in vacuo* to give **28** (80 mg, 96%). Purification by column chromatography was achieved by passing the crude compound through activated Alumina (neutral) with 2% MeOH in DCM (with a few drops of Et_3N). ^{1}H NMR (700 MHz, DMSO-d_6): δ = 15.46 (d, *J* = 5.1 Hz, 1H; N*H*), 9.29 (d, *J* = 4.6 Hz, 1H;), 8.84 (dd, *J* = 1.4, 4.6 Hz, 2H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.33 – 8.31 (m, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 7.98 – 7.95 (m, 2H), 7.87 (d, *J* = 4.6 Hz, 1H), 7.68 (dd, *J* = 1.4, 4.6 Hz, 2H), 6.36 (dd, *J* = 1.4, 7.4 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ = 150.5, 148.4, 147.5, 146.9, 145.2,

140.3, 140.2, 140.1, 136.6, 129.9, 126.1, 125.5, 125.2, 125.0, 124.8, 123.7, 122.4, 117.5, 111.5 ppm. HRMS (ESI/Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{21}H_{14}N_3O$ 324.1131; Found 324.1131. $C_{21}H_{13}N_3O \cdot 1.5H_2O$: calculated C 71.92, H 4.61, N 11.99; found C 72.23, H 4.33, N 12.03. IR (KBr disk): $\tilde{\nu}$ = 3433, 1627, 1614, 1571, 1525, 1504, 1188, 831 cm^{-1}.

Synthesis of 4,9-di(pyridin-4-yl)quinolino[7,8-*h*]quinoline (29): Dry DMF (20 mL) was added to a mixture of **17** (100 mg, 0.258 mmol), 4-pyridine pinacol ester (211 mg, 1.03 mmol), caesium carbonate (420 mg, 1.29 mmol) and the $Pd(PPh_3)_4$ catalyst (30 mg, 0.026 mmol) and stirred at 80 °C for 21 h. Water (50 mL) was added and the residue extracted with $CHCl_3$. The organic layer was washed with water (3 x 50 mL), dried with $MgSO_4$, filtered and dried *in vacuo*. The product was purified by recrystallisation from hot CH_2Cl_2 to give **29** (26 mg, 26%). Crystals suitable for X-ray crystallography were grown by slow evaporation of **29** in a 1:1:1 DCM:MeOH:$CHCl_3$ solvent mixture. ^1H NMR (700 MHz, $CDCl_3$) δ = 9.46 (d, *J* = 4.2 Hz, 2H; 2,11-*H*), 8.84 (dd, *J* = 1.6, 4.3 Hz, 4H; 2-Py-*H*), 7.99 (d, *J* = 8.8 Hz, 2H; 5,8-*H*), 7.94 (d, *J* = 8.8 Hz, 2H; 6,7-*H*), 7.54 (d, *J* = 4.3 Hz, 2H; 3,10-*H*), 7.51 (dd, *J* = 1.6, 4.3 Hz, 4H; 3-Py-*H*) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ = 150.2 (C2-Py, C2'-Py), 149.8 (C2, C11), 147.9 (C12a, C12c), 146.5 (C4, C9), 145.6 (C4-Py, C4'-Py), 135.5 (C4a, C8a), 128.1 (C6, C7), 126.9 (C12b), 125.7 (C5, C8), 125.6 (C6a), 124.6 (C3-Py, C3'-Py), 121.0 (C3, C10) ppm. HRMS (ESI/Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{26}H_{17}N_4$ 385.1448; Found 385.1447. $C_{26}H_{16}N_4 \cdot 0.8CH_2Cl_2$: calculated C 71.35, H 3.93, N 12.43; found C 71.35, H 3.79, N 12.76. UV-Vis ($CHCl_3$) λ_{max} (ε / L mol^{-1} cm^{-1}): 278 (58200), 359 (5820), 377 (6970) nm. IR (FT): $\tilde{\nu}$ = 3033, 1596, 1580, 1413, 1067, 871, 830, 775, 704 cm^{-1}.

Synthesis of 4,9-di(pyridin-3-yl)quinolino[7,8-*h*]quinoline (30): Dry DMF (25 mL) was added to a mixture of **17** (100 mg, 0.258 mmol), 3-pyridine boronic acid pinacol ester (211 mg, 1.03 mmol), caesium carbonate (420 mg, 1.29 mmol), $(t\text{-}Bu)_3PHBF_4$ (8 mg, 0.026

mmol) and $Pd_2(dba)_3$ (24 mg, 0.026 mmol). The suspension was stirred at 100°C for 20 h under an atmosphere of Ar. Water (50 mL) was added and the reaction mixture was basified with 6M KOH (40 mL) and extracted with $CHCl_3$. The organic layer was washed with water (3 x 50 mL), dried with $MgSO_4$, filtered and dried *in vacuo*. The product was purified by recrystallisation from hot DCE to give **30** (30 mg, 30%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.63 (d, *J* = 5.0 Hz, 2H; 2,11-*H*), 8.95 (br s, 2H; 2-Py-*H*), 8.90 (d, *J* = 4.0 Hz, 2H; 6-Py-*H*), 8.52 (d, *J* = 9.0 Hz, 2H; 5,8-*H*), 8.32 (d, *J* = 9.0 Hz, 2H; 6,7-*H*), 8.29 (d, *J* = 5.0 Hz, 2H; 3,10-*H*), 8.23 (d, *J* = 7.6 Hz, 2H; 4-Py-*H*), 7.79 – 7.76 (m, 2H; 5-Py-*H*) ppm. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 150.9 (C6-Py, C6'-Py), 150.2 (C2-Py, C2'-Py), 147.8 (C2, C11), 144.1 (C12a, C12c), 138.1 (C4-Py, C4'-Py), 136.5 (C3-Py, C3'-Py), 136.3 (C4, C9), 134.0 (C4a, C8a), 133.0 (C6a), 129.8 (C5, C8), 127.3 (C6, C7), 126.4 (C12b), 124.4 (C5-Py, C5'-Py), 124.0 (C3, C10) ppm. HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{17}N_4$ 385.1448; Found 385.1482.

Synthesis of 4-bromo-9-(pyridin-4-yl)quinolino[7,8-*h*]quinoline (31): Phosphorous oxybromide (266 mg, 0.928 mmol) was added to **28** (100 mg, 0.309 mmol) and stirred at 200 °C for 30 min under at atmosphere of Ar. A MeOH : CH_2Cl_2 solution (1:10, 33 mL) was added, the reaction mixture sonicated and then basified with 6M KOH (10 mL). Water (50 mL) was added to the reaction mixture and the organic layer collected. The aqueous layer was washed with MeOH : CH_2Cl_2 (1:10, 66 mL) and the combined organic layers were dried with $MgSO_4$, filtered, and dried *in vacuo* to give **31** (65 mg, 54%). ^{1}H NMR (700 MHz, DMSO-d_6): δ = 19.78 (s, 1H; N*H*), 9.67 (d, J = 4.3 Hz, 1H), 9.33 (d, J = 5.2 Hz 1H), 8.97 (s, 2H), 8.72 – 8.70 (m 1H), 8.66 – 8.65 (m, 1H), 8.62 (d, J = 5.2 Hz, 1H) 8.59 (dd, J = 1.2, 9.0 Hz, 1H), 8.33 (d, J = 5.2 Hz, 1H), 8.33 – 8.31 (m, 1H), 7.83 (s, 2H) ppm. ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6) δ = 152.1, 149.6, 147.9, 146.1, 143.6, 141.0, 139.0, 137.0, 130.7, 130.5, 129.2, 128.9, 127.8, 127.4, 127.3, 126.0, 124.7, 123.8, 116.2. HRMS (ESI/Orbitrap) m/z: [M

+ H]$^+$ Calcd for $C_{21}H_{13}{}^{79}BrN_3$ 386.0287; Found 386.0280.

Experimental determination of pK_{aH} values: A Perkin Elmer Lambda 40 or Agilent Cary 60 UV-Vis spectrophotometer connected with optical fibre cables to an external cell compartment inside a MBraun Unilab glovebox filled with argon (5.0 purity) was used for all UV-Vis spectrophotometric titrations. This setup ensured that moisture and oxygen contents during titrations were always under 10 ppm.

Triflic acid (Aldrich, 99+ %) and *tert*-butylimino-tris(pyrrolidino)phosphorane (Fluka, ≥97 %) were used to prepare acidic and basic titrant solutions. The concentrations of the titrant solutions were in the range of 1 – $5 \cdot 10^{-3}$ mol L^{-1} and the concentrations of the quinolinoquinoline derivatives and reference compounds were in the range of 1 – $14 \cdot 10^{-5}$ mol L^{-1}. Acetonitrile (Romil 190 SpS far UV/gradient quality) was used as solvent after drying with molecular sieves (3 Å) for at least 12 hours, which lowered the water content to a range of 2 – 6 ppm.

The determination of pK_{aH} values was based on the measurement of differences in the basicities of two bases. The first one was a quinolinoquinoline derivative and the second one a reference base with a previously known pK_{aH} values.[62] Both compound solutions were titrated individually and as a mixture in order to obtain the spectra of neutral and fully protonated as well as some partially protonated forms. The spectrophotometric data was used to calculate the dissociation levels (see equation 1) of conjugate acids of both bases in all mixtures formed during the titration. Using the dissociation levels (α) the differences in pK_{aH} values (ΔpK_{aH}) of the quinolinoquinoline and the reference base can be calculated according to equation 2.

$$\alpha = \frac{[B]}{[B] + [BH^+]} \quad (1)$$

$$\Delta \mathrm{p}K_{\mathrm{aH}} = \log \frac{\alpha_1(1-\alpha_2)}{\alpha_2(1-\alpha_1)} \quad (2)$$

Bases with previously published pK_{aH} values were used as reference bases.[62] All studied quinolinoquinolines were measured against at least two reference bases.

Two of the bases were converted to triflate salts and additionally purified for pK_{aH} measurements:

Compound **17** was suspended in MeCN and TfOH in MeCN was added dropwise until the colour of the solution did not change the colour anymore. The salt dissolved in MeCN completely. MeCN was then evaporated and compound **17** was recrystallized from MeOH to get light brown needle-shaped crystals **17**H^+TfO^-.

Compound **26** was dissolved in MeCN and TfOH in MeCN was added dropwise until the dark colour became light brown and of the solution did not change the colour anymore. The solvent and excess of TfOH were evaporated to dryness and the oily substance obtained was washed with Et_2O (dark oil was extracted). Portion of the compound (few crystals) suitable for pK_{aH} determination was crystallized out from CH_2Cl_2 at -15 °C. Most of the compound was recrystallized from the mixture of MeOH:water (4:1) to obtain yellow solid of **26**H^+TfO^-.

Computational details: Gas-phase proton affinities (PAs) and basicities (GBs) were calculated as protonation enthalpies and free energies, respectively, employing density functional theory (DFT) calculations at the B3LYP/6–311++G(3df,2p)//B3LYP/6–31+G(d,p) level and using the following reaction:

$$B_{(g)} + H^+_{(g)} \rightarrow [BH]^+_{(g)}$$

where B and BH^+ denote a base in question and its conjugate acid, respectively. Frequency analysis was used to calculate thermal corrections and validate the nature of the optimized stationary points. In this way, all thermodynamic values reported here correspond to a room

temperature of 298.15 K and a normal pressure of 1 atm. The choice of this methodology was prompted by its demonstrated accuracy in modeling acid/base features of various organic and inorganic systems.[7, 13, 63]

Implicit isodensity polarizable continuum model (IPCM) by Tomasi and co-workers[67] was used to account for the effect of the acetonitrile solution, and the corresponding pK_{aH} values were calculated using the empirical correlation:

$$pK_{aH}(MeCN) = 0.5751 \cdot PA(MeCN) - 144.1 \text{ units}$$

derived by Despotović and co-workers[68] in the case of 10 pyridine-based organic bases, and employing the recommended (IPCM)/B3LYP/6–311+G(d,p)//B3LYP/6–31G(d) model. In systems **15** and **20**, where the prototropic tautomerism in neutral bases causes a proton transfer from the –OH substituent to the pyridine nitrogen, and where the protonation formally occurs on the thus derived carbonyl oxygen atom, the pK_{aH} values were calculated through the proton transfer reaction: $B–H^+ + B_{REF} \rightarrow B + B_{REF}–H^+$, employing Schwesinger's vinamidine superbases as a reference base B_{REF} ($pK_{aH,EXP} = 29.2$).[69] All calculations were performed using the Gaussian09 software.[70]

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthesis of compounds **14** and **16**; ^{1}H NMR and ^{13}C NMR spectra for compounds **17** – **19**, **26** – **31**; general procedures and crystal data for X-ray crystallographic analysis of compounds **28**, **29** and **33**; reference and ΔpK_{aH} values for the determination of the experimental pK_{aH} values for compounds **2**, **13**, **15** – **17**, **20** and **26**; Cartesian coordinates for all computed structures together with their total electronic energies obtained at the B3LYP/6–

31+G(d,p) level of theory. (PDF).

Crystal data for compounds **28**, **29** and **33** (CIF).

Acknowledgements

The work at Tartu was supported by the Estonian Research Council grant PRG690 and by EU through the European Regional Development Fund under project TK141 "Advanced materials and high-technology devices for energy recuperation systems" (2014-2020.4.01.15-0011). The work at Zagreb was supported by the Croatian Science Foundation under grant number IP–2014–09–3386. R.V., I.D. and N.R. wish to thank the Zagreb University Computing Centre (SRCE) for granting computational resources on the ISABELLA cluster. P. G. P. is grateful to Massey University for the award of a doctoral scholarship to R. J. S. We would also like to acknowledge Prof. William Henderson from Waikato University for performing high resolution mass spectrometric analysis.

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