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Tautomeric Switching and Metal-Cation Sensing of Ligand-Equipped 4-Hydroxy-/4-oxo-1,4-dihydroquinolines

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Abstract: Novel 4-hydroxyquinoline (4HQ) based tautomeric switches are reported. 4HQs equipped with coordinative side arms (8-arylimino and 3-piperidin-1-ylmethyl groups) were synthesized to access O- or N-selective chelation of Zn^{2+} and Cd^{2+} ions by 4HQ. In the case of the monodentate arylimino group, O chelation of metal ions induces concomitant switching of phenol tautomer to the keto form in nonpolar or aprotic media. This change is accompanied by selective and highly sensitive fluorometric sensing of Zn^{2+} ions. In the case of the bidentate 8-(quinolin-8-ylimino)methyl side arm, NMR studies in CD_3OD indicated that both Cd^{2+} and Zn^{2+} ions afford N chelation for 4HQ, coexisting with tautomeric switching from quinolin-4(1*H*)-one to quinolin-4-olate. In corroboration, UV/Vis-monitored metal-ion titrations in toluene and methanol implied similar structural changes. Additionally, fluorescence measurements indicated that the metal-triggered tautomeric switching is associated with compound signaling properties. The results are supported by DFT calculations at the B3LYP 6-31G* level. Several X-ray structures of metal-free and metal-chelating 4HQ are presented to support the solution studies.

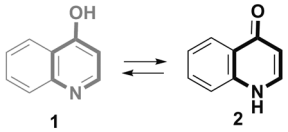
Keywords: molecular devices · quinolines · sensors · tautomerism · zinc

Introduction

Keto-enol-type tautomeric switches are to date a rather rare class of molecular switches, even though the proton shift occurring in equilibrating tautomerism is a fairly general phenomenon in organic chemistry that is relevant to a number of organic compounds.[1] Important examples of tautomerism include that of nucleic acids, which play a key role in base pairing, and that found in several enzymatic processes exploiting the phenomenon.[2] Accordingly, one could envision a class of less explored, conceptually novel, tautomeric molecules with significant supramolecular and biomimetic potential. The challenge is to introduce a "switch" into the molecule, in order to control its tautomeric states by means of some specific external input.[3] In practice this demands intelligent molecular design enabling molecules to respond to an input by energetically favoring one tautomeric state over the other.

An obvious reason for the existence of only a few tautomeric switches is the difficulty of controlling the related intramolecular proton transfer equilibria, while the processes are susceptible to environmental conditions such as solvent polarity and pH.[4] Optimally this sensitivity to media can be exploited as an input signal in control of adjustable tautomers. Recently, *para* azo phenol derivatives have been shown to exhibit adjustable tautomerism with their hydrazone form. Farrera et al. have shown that *para* azo (benzoic acid) phenol derivatives exist predominantly as aza or hydrazone tautomer in polar and nonpolar media, respectively, and each tautomer exhibits a distinct bioaffinity.[5] Antonov et al. have used similar compounds, namely, *para* azo (phenyl) phenol *ortho* piperidines, to demonstrate the general concept that azo-hydrazone tautomerism can be controlled by the proton or a metal equivalent which leads to signaling effects.[6]

Our research interest lies in the generation of switch control for 4-hydroxyquinoline (4HQ, **1**)–quinolin-4(1*H*)-one (**2**) tautomerism (Scheme 1). Their tautomeric behavior is analogous to the structurally parent compounds 4-hydroxy pyridines (bold in Scheme 1), which are known to be in tautomeric equilibrium with their oxo form, 4-pyridone, with the former prevailing in polar media and in the crystal,



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Scheme 1.

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while the latter are detected in the gas phase and under dilute conditions in nonpolar media.[7] Substituent effects such as polarization of the aromatic ring by electron-withdrawing atoms or groups have been shown to affect this equilibrium.[7a] For 4HQ it was suggested that electron-withdrawing groups at C-2 or hydrogen-bond acceptors at C-3 could favor the enol form in solution.[8]

In a similar way, tautomeric duality has been recognized among natural product 4HQ derivatives; for example, kynurenic acid (4-hydroxyquinoline-2-carboxylic acid) is generally considered to be in its phenol form and even crystallized in such form,[9] but it has been shown to exist chiefly in the keto form in polar medium (DMSO).[10] In contrast, acridone (acridin-9(10*H*)-one) was found solely in the oxo form in both $CDCl_3$ and DMSO.[11] The phenol form is assigned to *O*-methylated 4HQ derivatives (e.g., dictamnine), whereas the quinolone form is assigned to *N*-alkylated compounds.[12] The activity of a number of synthetic *N*-alkylated 4-quinolone-based antibiotic drugs and antiviral agents can be linked to the oxo form.[13] On the other hand, some phenol forms assigned to 4HQ amide derivatives have shown antiviral activity in DNA polymerase inhibition.[14] Although in the above-mentioned cases the activity may genuinely arise in large part from other structural properties, the distinct tautomers have different physical and chemical properties that can be expected to correlate with, for example, bioactivity. This raises the issue of whether external control could regulate related activity in tautomerically switchable 4HQ.

From the photophysical point of view, 4HQ are attractive because quantum chemical calculations have indicated that each tautomer is clearly electronically divergent and leads to visibly distinct luminescence properties.[15] Notably, *O*-alkylated 4HQ have been successfully used as platforms in building fluorescent probes for Zn^{2+} and Cd^{2+} ions.[16]

In this study our approach is to functionalize 4HQ with two ligand side arms that act either as hydrogen-bond acceptors or metal chelators in co-coordination with quinoline O or N electron pairs (Figure 1). The metal chelation is supposed to freeze the tautomer in which chelation is energetically favoured and thereby induce controlled tautomer switching.

We chose 8-arylimino-3-(piperidin-1-ylmethyl)quinolinols (**3**) as target structures (Scheme 2) to test this scenario (Figure 1). The compounds were expected to be synthetically accessible from 8-bromoquinolin-4-ol (**5**) in a straightforward manner. The imino group at C-8 is π-conjugated with the quinoline and therefore is expected to strengthen individual signaling properties for each tautomer, which could facilitate monitoring by NMR, absorption, and fluorescence spectroscopy. On the contrary, the piperidin-1-ylmethyl moiety is a non-π-conjugated electron-pair donor, which, in addition to its coordination ability, is anticipated to also quench quinoline fluorescence when free of proton or metal coordination.[17]

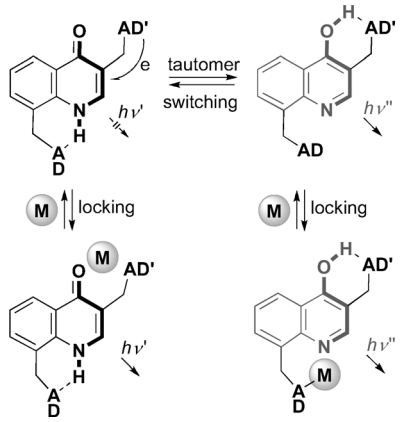
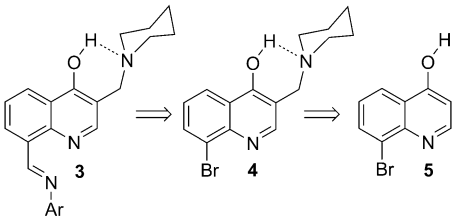


Figure 1. Tautomer switching and locking scenario for ligand-equipped 4HQ by site-selective metal chelation, where *hν′* and *hν″* denote expected fluorescence signalling under light irradiation (*hν*). **M** = metal, **AD** = hydrogen-bond acceptor/electron-pair donor, **AD′** = hydrogen-bond acceptor/electron-pair donor/electron donor.



Scheme 2.

Results and Discussion

Computational Studies: To theoretically assess the envisioned switchability (Figure 1) and screen potential synthetic targets, we geometry optimized several quinoline derivatives equipped with 8-arylimino and 3-piperidin-1-ylmethyl groups at the DFT level using $ZnCl_2$ and $CdCl_2$ salts as models for trigger inputs (Table 1).

Inspection of the energetics of tautomers **6–10** in Table 1 shows a rather clear trend; electron-rich imines favour H-bonding of the imine to amine NH, thus resulting in the oxo form, whereas electron-poor substitution slightly promotes the phenol form, in which the piperidine nitrogen atom acts as a hydrogen-bond acceptor. In contrast, the bidentate 8-iminoquinoline in compound **11** favors N-site chelation of the metal and therefore the phenol form.

It has been observed for 4HQ that the large dipole moment calculated in vacuum favours a specific tautomer in polar media.[18] In this light the oxo form should be preferable for metal complexation of electron-rich imines **6–8**, while electron-poor imines should favour N-site chelation and the phenol form (Table 1).

Ligand function test for solely 8-imino- and 3-piperdinyl-functionalized 4HQ: First, we synthesized simple 8-phenyl-3-(piperidin-1-ylmethyl)quinolin-4-ol (**12**) as reference com-

Table 1. DFT B3LYP/6-31G* geometry optimized 4HQ tautomer energies with and without metal salts (lanl2dz basis set was applied for Zn and Cd).

Compound	R	Metal salt M	Relative tautomer E [kcal mol^{-1}]	Dipole moment [D]	Relative tautomer E [kcal mol^{-1}]	Dipole moment [D]
		–	−1.4	5.02	0	6.6
6		$ZnCl_2$	−6.1	17.32	0	10.9
		$CdCl_2$	−7.7	16.75	0	10.9
		–	−1.7	6.55	0	6.7
7		$ZnCl_2$	−6.3	19.13	0	10.7
		$CdCl_2$	−8.0	18.51	0	10.9
		–	−2.3	8.67	0	4.7
8		$ZnCl_2$	−6.3	21.82	0	8.2
		$CdCl_2$	−8.1	21.25	0	8.5
		-	0	1.43	−0.55	11.9
9		$ZnCl_2$	−5.5	11.16	0	16.0
		$CdCl_2$	−7.2	10.53	0	15.7
		–	0	1.62	−1.56	12.2
10		$ZnCl_2$	−5.1	10.85	0	16.5
		$CdCl_2$	−8.1	10.18	0	16.0
		–	−3.3	7.44	0	6.1
11		$ZnCl_2$	0	17.32	−0.25	6.5
		$CdCl_2$	0	19.58	−0.97	7.6

pound. This compound was studied in order to probe whether a hydrogen-bonding acceptor alone at C-3 could favour the phenol tautomer. Unfortunately, due to its poor solubility in nonpolar solvents, reliable tautomer characterization by NMR methods was not feasible in toluene. However, an adequate amount of compound was dissolved in toluene to for monitoring by UV/Vis spectroscopy when titrated with methanol (Figure 2). The observed changes in the spectra can be explained by increase in polarity and hydrogen-bonding interactions with methanol. Owing to the increasing polarity of the medium, the changes in the spectra may be interpreted as arising from changes in electronic structure, which in turn are caused by the isomerization of phenol to keto form. In support of this hypothesis, the spectral shapes are in good accordance with 4HQ tautomeric forms identified by photospectroscopic studies of inonization constant,[19] which underpin the switch from phenol to keto form due to the increase in solvent polarity.

Computational studies show that the phenol form of **12** is −3.2 kcal mol^{-1} more stable than the keto form, and their dipole moments are 4.84 and 5.79 D, respectively. This suggests that the molecule would exists in phenol form in nonpolar media, whereas the more polar keto form could be favoured in polar environments.

Compound **12** was additionally titrated with $ZnCl_2$ in toluene and monitored by UV/Vis spectroscopy to probe whether similar switching could be induced by metal ions (Figure 3). The titration indicated that this was indeed the case; the spectral changes were similar and even more visible, and saturation was reached when one equivalent of metal ions was added. Together these titrations imply that for **12** both an increase of solvent polarity and metals ion are capable of inducing switching from phenol to keto tautomer.

With the aim of improving the low solubility of **12** in nonpolar or aprotic solvents, compound **13** was synthesized with flexible dipicolylamine (Dpa) moiety. In UV/Vis titration experiment with $ZnCl_2$ in toluene, this compound showed similar behaviour to compound **12** (Supporting Information). Compound **13** is sufficiently soluble in CD_3CN to perform ^{1}H NMR-monitored titration with $Zn(ClO_4)_2$ (Figure 4). Addition of metal ions induced prominent spectral changes. First, development of an AB system (H3^1) from the original singlet on addition of metal ions indicates that the Dpa moiety chelates the Zn ion, as expected. Second, a broadened proton signal at 9.5 ppm

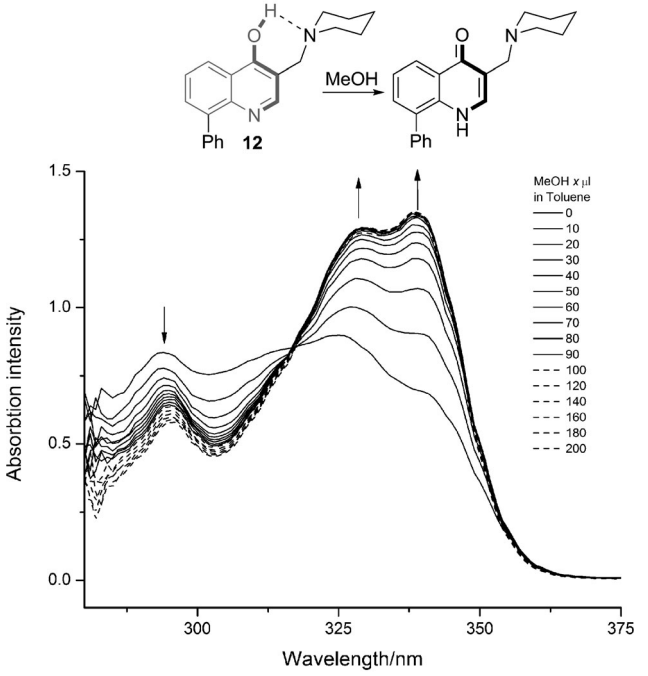


Figure 2. UV/Vis-monitored titration of **12** with MeOH (0–200 µL) in toluene (0.1 mM in 2 mL).

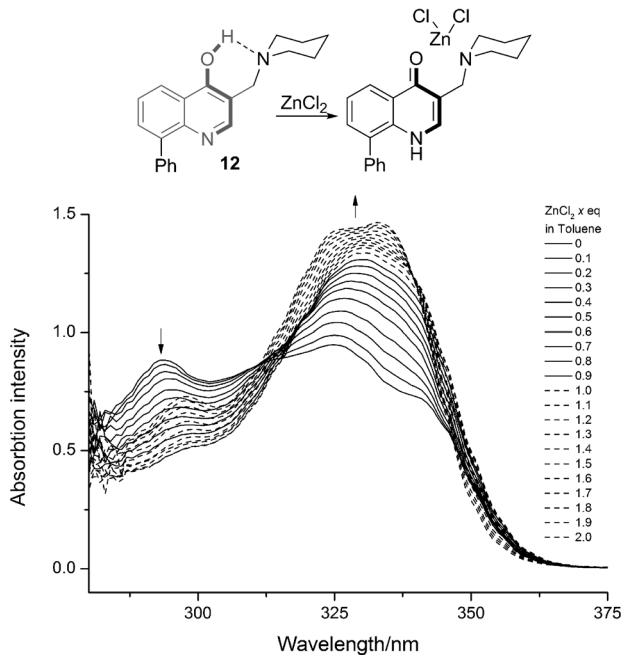


Figure 3. Titration of **12** with $ZnCl_2$ (0–2 equiv) in toluene (0.1 mM in 3 mL).

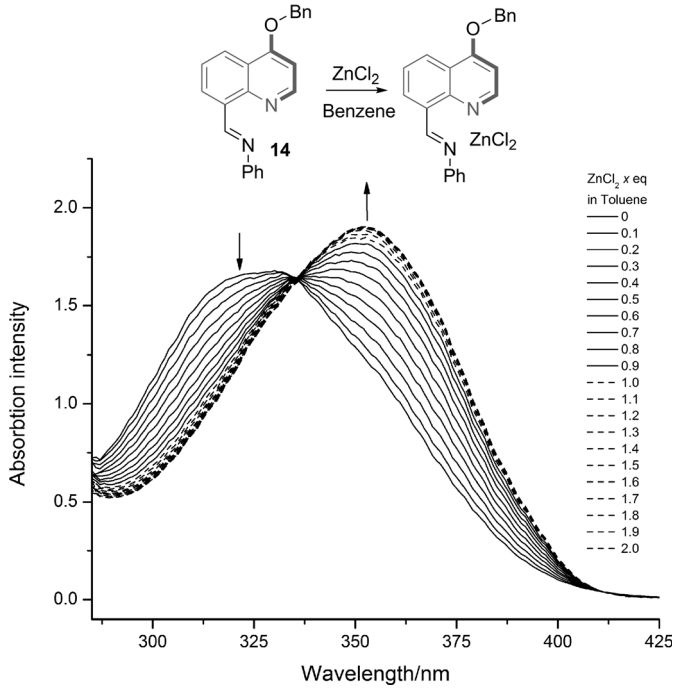


Figure 5. UV/Vis-monitored titration of **14** with $ZnCl_2$ (0–2 equiv) in toluene (0.1 mM in 3 mL).

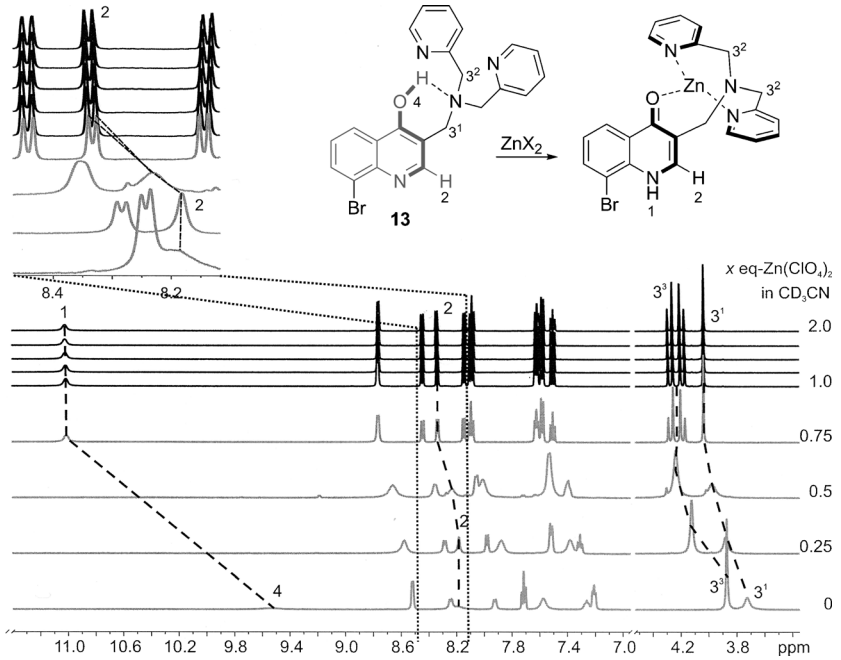


Figure 4. ^1H NMR-monitored titration of **13** with $Zn(ClO_4)_2$ (0–2 equiv) in CD_3CN.

(H4) shifts 1.5 ppm to lower field (H1) on addition of one equivalent of Zn. Third, proton resonance H2 is transformed from a singlet into a doublet after addition of one equivalent of metal ions to the system. The COSY spectrum confirmed that the doublet coupling is induced by NH proton H4. Together these changes indicate switching from phenol to keto tautomer on addition of metal ions (Figure 4).

To examine whether the arylimine moiety can chelate metal ions we synthesized *O*-benzyl-protected 4HQ derivative **14**. As expected, this compound chelated Zn ions, as reveled by a clearly redshifted signal in metal-ion titration (Figure 5). The metal chelate structure was also successfully characterized by XRD (Figure 6). The complex showed intense fluorescence response, but this could be observed only in the solid phase.[20]

Probing compounds 6, 7, 8, 10, and 11 for metal-induced switching: The NMR spectroscopic studies showed that for all the bidentate compounds **6**, **7**, **8**, **10** and **11**, the keto form is the prevailing tautomer in both $CDCl_3$ and CD_3OD solutions. In chloroform, this was indicated by the doublet signal of the proton at C-2, resulting from coupling to the vicinal amine proton; in methanol, proton exchange with the solvent masked the phenomenon, although chemical shifts were overall similar. Moreover, the chemical shifts in $CDCl_3$ in the range 12–14 ppm also indicated that the amine proton was involved in hydrogen-bonding with the imine, as predicted by the computational study.

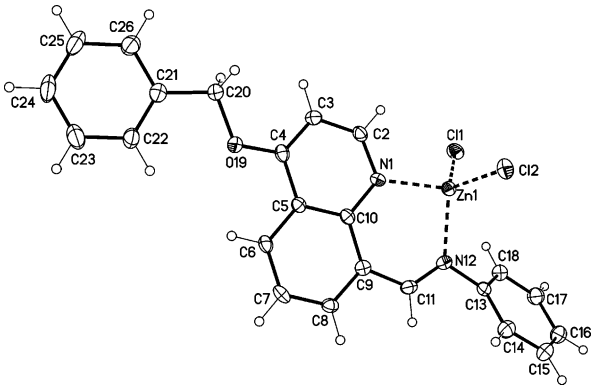


Figure 6. Molecular structure of one of the crystallographically independent molecules of **14**. Displacement parameters are drawn at 50% probability. Selected bond lengths [Å]: N1–C2 1.333(4), C2–C3 1.389(4), C3–C4 1.380(4), C4–O19 1.329(3).[21]

In the case of compound **8**, we succeeded in obtaining single crystals for X-ray characterization (Figure 7). The solid-state structure is in good agreement with the computational predictions and NMR results: as expected, the compound is in the keto form and the imine nitrogen atom shows strong hydrogen bonding to the NH proton (N1H···N12 1.91(3) or 1.93(3) Å, measured for the dimer in the crystal unit cell).

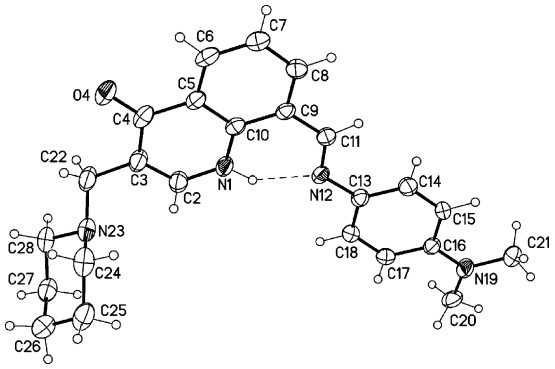


Figure 7. Molecular structure of one of the crystallographically independent molecules of **8**. Displacement parameters are drawn at 50% probability. Selected bond lengths [Å]: N1–C2 1.353(4), C2–C3 1.354(4), C3–C4 1.445(4), C4–O4 1.251(4).[21]

Monodendate aryl imines **6**, **7**, **8**, and **10** were first titrated with metal ions and monitored by UV/Vis absorbance. In methanol, both the Zn^{2+} and Cd^{2+} ion titrations showed only small changes overall (1–20 nm), of which the more pronounced occurred for Zn^{2+} ions interacting with electron-rich aryl imines **7** and **8** (Supporting Information). However, as shown in Figure 8, use of toluene led to drastic spectral changes when these imines were titrated with $ZnCl_2$. Unfortunately, these data were not conclusive; therefore, we used computational approach to estimate the energies of the different tautomers (Table 1), and to explain the observed spectral behaviour. Scheme 3 illustrates, on the left, compound **8** in the keto form in toluene, with the imino

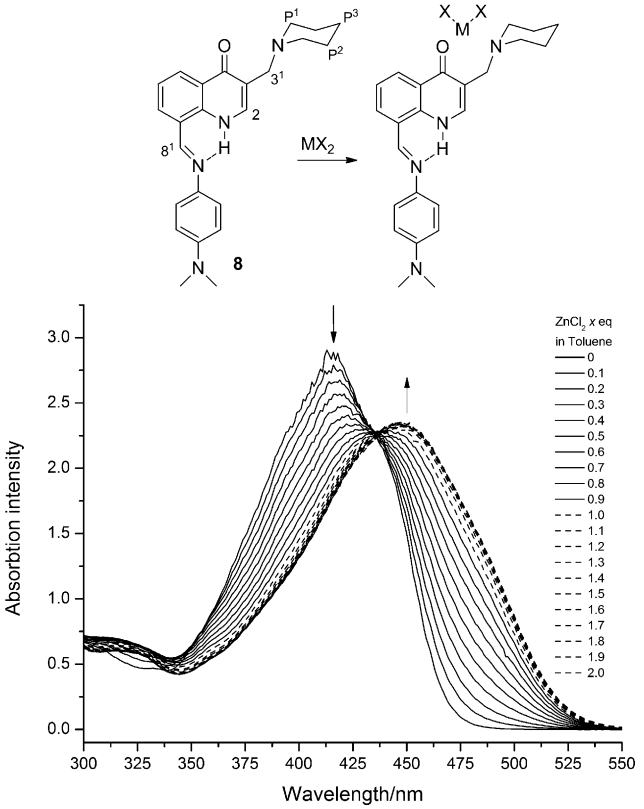
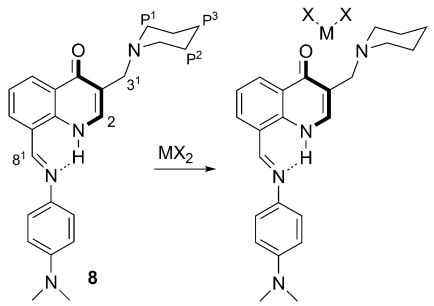


Figure 8. UV/Vis-monitored $ZnCl_2$ titration (0–2 equiv) of **8** in toluene (0.1 mM in 3 mL).



Scheme 3.

group strongly hydrogen-bonded to the amino group, while on the right the metal ion is chelated by the O site as titration progresses. This implies that, under these conditions, the tautomeric equilibrium is shifted towards the keto form, which undergoes regioselective metal chelation.

Unfortunately, the poor solubility of the Zn complexes in both methanol and toluene did not allow for clear ^{1}H NMR spectra. Nevertheless, when titration was successfully performed with $Cd(OAc)_2$ in CD_3OD, only minor changes in the NMR spectra were observed on addition of metal ions, as exemplified in Figure 9. Interestingly, the induced changes appeared on the O site of the molecule: H-3^1 and H-P^1 and H-6 of the piperidine moiety experienced deshielding effects of 0.1–0.3 ppm, which are most likely induced by metal chelation.

In fluorescence studies, monodentate aryl imines **6**, **7**, **8**, and **10** showed selective emission response for Zn^{2+} ions (Figure 10). A high quantum yield was measured for the $ZnCl_2$ complex of **6** (Φ_F = 0.205) in toluene and somewhat lower in MeOH (Φ_F = 0.093). The emission maxima of **6** were only weakly dependent on solvent or metal chelation; the emission maximum was 517 nm in toluene, while with $ZnCl_2$ and $Cd(OAc)_2$ blue shifts to 514 and 511 nm, respectively, occurred. When methanol was employed, the metal-free emission maximum was at 522 nm, and Zn and Cd ions caused blue shifts to 521 and 512 nm, respectively. The hypsochromic shifts in the absorption maximum of **6** on changing from toluene to methanol and addition of metal ions were even more pronounced. For **7** the trends for metal-ion additions were similar. However, overall inspection of absorption and emission maxima in Table 2 for compounds **6**, **7**, **8** and **10** does not fully confirm that these values could provide information about tautomeric equilibrium.

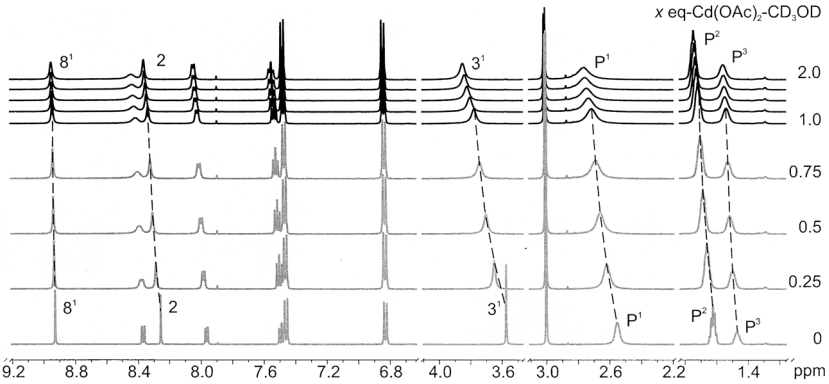


Figure 9. ^{1}H NMR monitored titration of **8** with $Cd(OAc)_2$ (0–2 equiv) in CD_3OD. See proton numbering in Scheme 3.

We could not obtain crystals of metal complexes **6**–**10** suitable for X-ray analysis, but we were able to isolate single crystals of **6** from a reaction with $Zn(ClO_4)_2$ in MeOH. The X-ray structure shows formation of exceptional inclusion complexes in the crystal unit cell: two molecules in the keto form incorporate one perchlorate anion, with both piperidine nitrogen atoms still protonated (Figure 11). Remarkably these protons are not hydrogen-bonded to the keto group in close proximity. However, this situation is probably different in solution in the absence of crystal packing forces. It could be speculated that the proton on the O site of 4HQ would then favour the keto form by hydrogen-bonding interactions.

Overall, 8-aryl amine compounds **6**, **7**, **8**, and **10** did not show tautomeric changes on metal-ion coordination; the prevailing keto form is instead locked by O-site metal-ion chelation. With the exception of compound **10**, this was predicted by computationally modelling (Table 1). Nevertheless, the emission studies show that the compounds are selective fluorescence probes for Zn^{2+} ions: they are quantum-efficient in non-polar media, but still operative in protic polar media.

Study on compound 11: UV/Vis-monitored titration of **11** with both Cd^{2+} and Zn^{2+} ions showed very clear spectral changes in both methanol and toluene. Figure 12 depicts the titration with $ZnCl_2$ (0–2 equivalents) in methanol. Encouragingly, com-

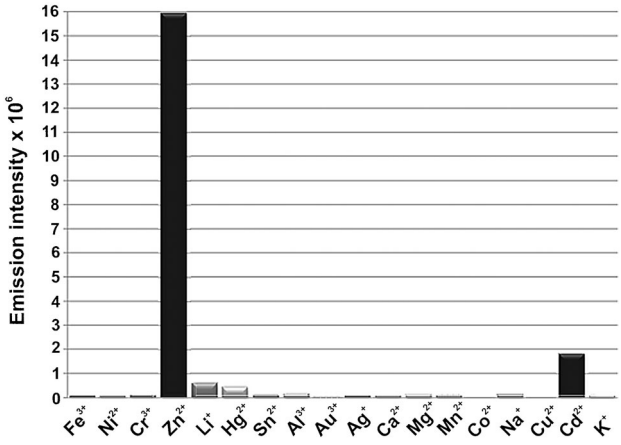


Figure 10. Fluorescence responses of compound **6** to metal ions.

Table 2. Emission, absorption maxima and selected quantum yields measured in methanol and toluene for compounds **6**–**8**, **10**–**12** and **14**.

Compound + metal salt	Toluene			MeOH		
	λ_{abs} [nm]	λ_{em} [nm]	Φ_F	λ_{abs} [nm]	λ_{em} [nm]	Φ_F
6	390	517	–	368	522	–
+ $ZnCl_2$	384	514	0.205	369	521	0.093
+ $Cd(OAc)_2$	378	511	–	366	512	–
7 + $ZnCl_2$ + $Cd(OAc)_2$	390	504	–	377	513	–
	404	501	0.043	378	510	0.024
	385	500	–	377	502	–
8 + $ZnCl_2$ + $Cd(OAc)_2$	416	553	–	413	576	–
	447	559	0.061	432	576	0.001
	421	–	–	416	–	–
10 + $ZnCl_2$ + $Cd(OAc)_2$	387	554	–	380	552	–
	375	560	0.108	373	538	0.002
	392	–	–	377	–	–
11 + $ZnCl_2$ + $Cd(OAc)_2$	385	562	–	373	560	–
	429	567	0.114	415	565	0.017
	371	565	–	413	556	–
12 + $ZnCl_2$ + $Cd(OAc)_2$	325	398	–	–	–	–
	333	–	–	–	–	–
	–	–	–	–	–	–
14 + $ZnCl_2$ + $Cd(OAc)_2$	325	–	–	328	–	–
	350	–	–	340	–	–
	331	–	–	330	–	–

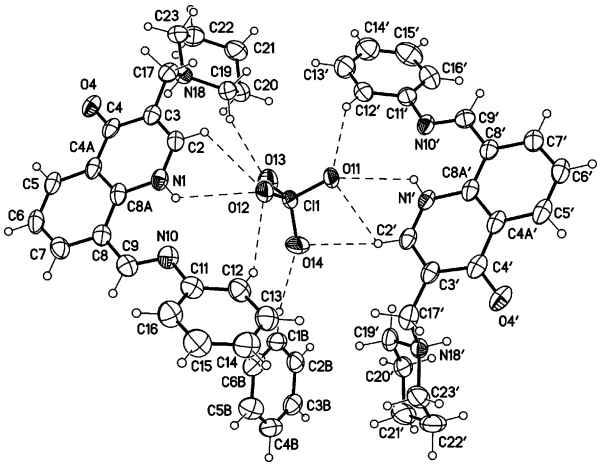


Figure 11. Molecular structure of one of the crystallographically independent molecules of the dimeric inclusion complex of **6** and $HClO_4$ (the disordered second ClO_4^- anion is omitted for clarity; displacement parameters are drawn at 50% probability). Selected bond lengths [Å]: N1–C2 1.329(5), C2–C3 1.358(5), C3–C4 1.418(5), C4–O4 1.256(4).[21]

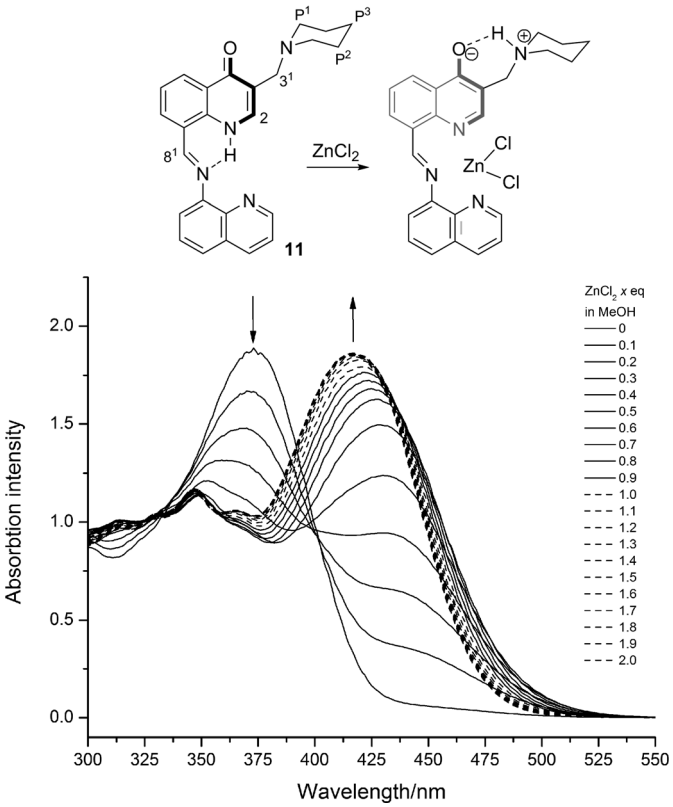


Figure 12. UV/Vis-monitored $ZnCl_2$ titration (0–2 equiv) of **11** in MeOH (0.1 mM in 3 mL).

plete spectral changes were reached after the addition of the first equivalent of the zinc salt. Comparison of this titration to that of **8** in toluene shows that the changes in spectral line shape are more pronounced; individual additions of 0.1 ion equivalents have substantial effects, not only by red-shifting the absorption maxima, but also by reshaping the spectral profile.

To find out whether the metal ion genuinely induces the desired structural change, we repeated the titrations with Zn^{2+} and Cd^{2+} ions, monitoring by ^1H NMR in CD_3OD (Figure 13). For Zn^{2+} addition, the spectral changes were partially indefinite (Supporting Information) and precipitation of the metal complex was observed. However, when Cd^{2+} was used, we could observe clear tautomer-related spectral changes that occurred upon addition of the first ion equivalent; at the start of titration a set of aromatic protons disappeared and, on subsequent additions, appeared again, but with different chemical shifts and coupling patterns. Characteristically, imine proton H-8^1 is deshielded (0.3 ppm) by metal addition, which implies N-site chelation. Unexpectedly, the piperidine moiety N-vicinal protons 3^1 and P^1 were both substantially deshielded, shifted by 0.6 ppm to low field. However, these large shifts seem to imply N protonation rather than metal chelation. With the aid of 2D NMR experiments (NOESY, HSQC and HMBC) we were able to characterize **11** with one equivalent of $Cd(OAc)_2$ as N-site-chelated phenol tautomer.

To obtain final confirmation for metal chelation of **11**, we isolated single crystals of the $Zn(ClO_4)_2$ complex with **11** (Figure 14). The X-ray structure confirms N-site chelation, with bond lengths of about 2 Å between the Zn centre and the three coordinating nitrogen atoms. A comparison of the key bonds lengths (N1–C2, C2–C3, C3–C4) of crystalline **11** with similar values in both tautomer-like phenol (**14**) and "neutral" keto (**8**) forms clearly indicates a better correlation of bond lengths and similar degree of electronic delocalization of **11** to phenol form **14**. The corresponding bond lengths in the keto form (**8**) can be associated to π-bonding systems with a higher degree of electronic localization. On the other hand, the C4–O4 bond

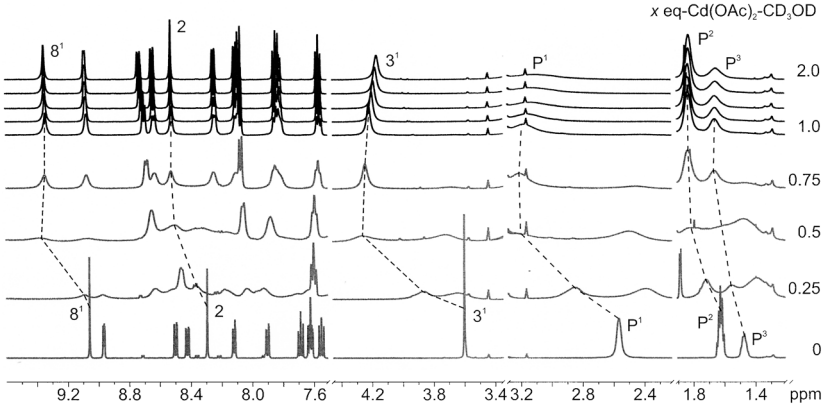


Figure 13. ^1H NMR-monitored titration of **11** with $Cd(OAc)_2$ (0–2 equiv) in CD_3OD. See proton numbering in Figure 12.

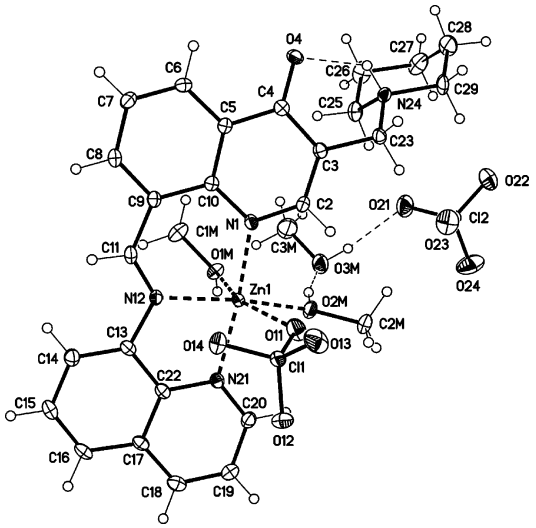


Figure 14. Molecular structure of **11**+$Zn(ClO_4)_2$. Selected bond lengths [Å]: Zn1–N1 2.026(2), Zn1–N12 2.076(2), Zn1–N21 2.062(2), N1–C2 1.329(3), C2–C3 1.363(4), C3–C4 1.399(4), C4–O4 1.266(3), O4–H24 2.11(1).[21]

length (1.266(3) Å) in **11** differ to the literature values typical for keto (1.210(8) Å) and phenol (1.364(11) Å) tautomers, but instead it matches rather well that of carboxylate anion (C–O 1.254(10)).[22] Strikingly, also the C4–O4 bond length of 1.251(4) Å in keto form (**8**) may be attributed to some ionic nature that probably arises from hydrogen-bonding interaction between the imine and amine hydrogen (Figure 7). On this basis, after examination of the crystal structure of complex **11**, we can establish that the ligand is present in the neutral betaine structure, whereby the negative charge is localized over the phenolate oxygen (O4) atom and is stabilized by the neighboring aminium cation (N24). This clearly indicates that whilst the 4HQ ring structure in complex **11** can be identified as phenolic, the structures of neutral **8** and protonated **6** can described as keto-type isomers. Indeed, this switterionic complex structure of **11** is also in agreement with the NMR studies regarding the piperidine nitrogen atom, which turns out to be protonated.

All together, compound **11** acts as a metal ion adjustable tautomeric switch. Also, a fluorescence measurement (Table 2) showed strong emission for the Zn complex, which makes the compound behave according to the right pathway in Figure 1. The metal-ion titration experiments were carried out with different counter-ions (chloride, acetate and perchlorate), and all displayed similar behaviour in the spectroscopic experiments.

Conclusion

We have demonstrated that 4HQ equipped with suitable ligand side arms can co-chelate Zn^{2+} and Cd^{2+} ions with 4HQ keto or amino (pyridine-type) moieties, and adjust thereby the associated tautomeric equilibria. For 4HQ **12** with C-3-attached piperidin-1-ylmethyl monoligand, it was shown in nonpolar media that O-site metal chelation caused a switch from the tautomeric phenol form to the keto form. Moreover, the ^{1}H NMR-monitored titration of compound **13** with Zn salt showed spectral changes from phenol to keto tautomer upon metal-ion addition. However, when the piperidine-equipped compound is additionally armed with a monodentate arylimino group at the C-8 position, it seemed that the chelation will not take place at the N site, and the prevailing oxo tautomer was rather locked by O chelation. Bidentate aryl imino, 8-(quinolin-8-ylimino)methyl quinoline derivative **11** evidenced that metal chelation not only froze the tautomerism, but also induced unambiguous switching from keto to phenolate tautomeric state.

Additionally, the metal-chelation experiments showed that many of the synthesized 4HQ can be utilized in selective Zn^{2+} fluorescence sensing. A future challenge in this area is to develop and study the 4HQ or analogues switches in such a way that the free chelate site of moiety will participate in adjustable manner for supramolecular binding or specific biological function.

Experimental Section

Synthesis of 6–11: Compounds **6–11** were synthesized by following the retrosynthetic plan depicted in Scheme 2. The imine bond of compound **9** turned out to be unstable under ambient conditions, and hence this compound was excluded from the experimental studies. The formal starting compound 8-bromoquinolin-4-ol (**5**) was synthesized according to a literature procedure.[23] Compound **8** was functionalized with piperidine to obtain **4** by modifying the existing Mannich reaction procedure[6a] to be free from catalytic acid additives. For other compounds literature references were followed strictly or with minor changes. The synthetic details and characterization compounds are described in the Supporting Information.

UV/Vis-, fluorescence- and ^{1}H NMR-monitored titrations for compounds **6**, **7**, **8**, **10**, **11**, **12** and **13** with Zn and Cd ions are presented in the Supporting Information.

Computational studies: Performed with Gaussian 09 software[24] by the B3LYP method at the 6-31G* level, except that the lanl2dz basis set was applied for Zn and Cd atoms. The calculations presented in Table 1 were run in the gas phase. The level of theory was shown be adequate for the comparison of tautomers by performing test calculations on 4HQ with more advanced basis sets or with implicit solvation models. In the former case it was found that the keto form of 4HQ lies at 4.4 kcal lower energy, while the IEFPCM implicit solvent model increases the energy difference in favour of the keto tautomer to 5.5, 6.0 and 6.6 kcal mol^{-1} for toluene, chloroform and water, respectively. For the latter case, calculations in the gas phase with 6-31+Gd,p and 6-311+G2d,2b basis sets gave 3.25 and 3.28 kcal mol^{-1}, respective, in favour of the keto tautomer.

Crystallographic data: The structures reported in this work have been deposited with the CCDC.[21] Crystallographic experimental data are presented in the Supporting Information.

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Molecular Switches

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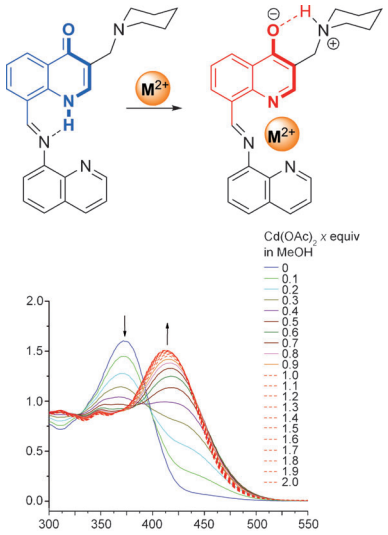
Tautomeric Switching and Metal-Cation Sensing of Ligand-Equipped 4-Hydroxy-/4-oxo-1,4-dihydroquinolines



Switching tautomers: Transformation of 4-hydroxyquinolines (4HQ) into novel tautomeric switches is described. 4HQ are equipped with ligand moieties at C-8 and C-3 positions to achieve metal ion adjustable control of keto-phenol tautomerism. In the case of the 8-(quinolin-8-ylimino)methyl side arm, metal ion induced tautomeric switching from keto to phenolate form was observed in nonpolar and polar media (see figure). Both O- and N-site-directed chelation resulted in selective Zn^{2+} fluorescence sensing.

