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Colorimetric detection of trace water in tetrahydrofuran using *N*,*N*'-substituted oxoporphyrinogens

Low concentrations of water can be colorimetrically detected in tetrahydrofuran enabling potential improvements in reaction yields and at the same time improving laboratory safety. This work opens the way for simple colorimetric tests of any organic solvents used for water-sensitive reagents.

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COMMUNICATION

Colorimetric detection of trace water in tetrahydrofuran using N,N'-substituted oxoporphyrinogens[†][‡]

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Oxoporphyrinogens (OxPs) bind water molecules at pyrrolic NH and quinonoid carbonyl groups leading to visible colour changes due to variation in the π -electronic structure of OxPs. Introduction of hydrophilic substituents at two pyrrole NH groups improves sensitivity to H₂O, and one OxP derivative is a colorimetric indicator of trace H₂O (~50 ppm) in THF.

Quantitative analysis of H₂O in organic solvents is important in fundamental and industrial applications¹ especially in polar aprotic solvents in which water is miscible and which are used as solvents for water-flammable reagents (e.g., alkali metals, organolithiums, Grignard reagents).² The Karl-Fischer method³ permits detection of H₂O down to the ~ 1 ppm level but it can be inconvenient due to instrumental requirements and toxic reagents (*i.e.*, methanol, I_2 and SO_2). Alternatively, use of a dye molecule as an H₂O-indicator would faciltate H₂O detection in organic solvents. Fluorescence of some dyes is quenched (or emission spectra change) in response to variations in H₂O concentration⁴ with one such molecule enabling detection of ~20 ppm H₂O in some solvents, ^{4b} which approaches Karl-Fischer sensitivity. However, the accuracy of fluorescence analysis can be detrimentally influenced by many factors including other quenchers, photobleaching, concentration, temperature, etc. In contrast, colorimetric analyses of H2O using solvatochromic dyes is generally more stable although sensitivities may be lower (~1000 ppm H_2O) as colour changes depend on the variation of total solvent polarity.⁵

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Fig. 1 Chemical structures of oxoporphyrinogens (OxPs) 1–6 used for colorimetric detection of H_2O in THF (Symbols denote the assignment of ¹H-NMR peaks of OxP 2 shown in Fig. 3.).

Here we show that oxoporphyrinogens (Fig. 1), a class of porphyrinoid, are available as colorimetric indicators for trace contaminating H₂O in tetrahydrofuran (THF) to a level of ~50 ppm by means of UV-Vis spectroscopy. Investigations conducted using ¹H-NMR spectroscopy and theoretical calculations reveal that OxPs bind H₂O molecules at both pyrrolic NH and quinonoid C=O groups, varying the π -electronic structure and leading to visible colour changes. Even though the detection limit of H₂O by these OxP derivatives is somewhat low compared to the best fluorescent probe, the use of OxP has great advantages of (i) the UV-Vis spectrum being easy to obtain and more stable than the fluorescence spectrum; (ii) the sensitivity of OxP to H₂O is variable by synthetic modifications; (iii) OxP can be reused without chemical change or photobleaching.

OxP belongs to the calixpyrrole family⁶ and contains a cyclic tetrapyrrole conjugated with quinonoid moieties at its *meso*-positions. OxP binds a variety of guest molecules at its pyrrolic NH's as well as at the quinonoid C=O groups. In contrast to typical calixpyrroles, OxPs have a strong absorption in the visible light region due to π -conjugation between tetrapyrrole and quinonoid substituents. This conjugation is sensitive to binding of guests to OxPs and these compounds have been reported to behave as probes for anions or solvents,⁷ and enantiomeric excess.⁸ For solvents, it was thought that major interactions between OxP derivatives and solvents occurred with pyrrolic NH groups acting as H-bond donors^{7a,9} and that *tert*-butyl groups largely prevented any strong intermolecular interactions involving the C=O groups.¹⁰

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Fig. 2 (a) Colour variation of OxP 5 in anhydrous and hydrated THF. (b) Variation in absorption spectra of OxP 5 in response to H₂O concentration (THF, $[5] = 3.5 \times 10^{-6}$ M, 1 cm cell). Inset: magnified spectra around 500 nm. (c) and (d) Variation of absorption at 507 nm and 600 nm for OxP 5 in response to H₂O concentration in THF. H₂O concentration is classified into three regions in (d); green (anhydrous: $H_2O < 50$ ppm), yellow (normal: 50 ppm $< H_2O < 500$ ppm), and red (hydrated: 500 ppm < H₂O) according to the guaranteed H₂O level of commercially available THF.

OxP derivatives 1-6 (Fig. 1) were synthesized according to reported methods9 and investigated as colorimetric H2O indicators in THF. OxPs 1-5 demonstrate visible colour changes from red-purple to blue-purple by hydration of THF (Fig. 2a). On the other hand, OxP 6, which lacks pyrrolic NH due to full N-substitution, remained red-purple even after addition of a large excess of H₂O. As shown in Fig. 2(b), addition of H₂O to an anhydrous solution of OxP in THF attenuates the absorption at 507 nm while increasing the absorption intensity at 600 nm and 750 nm. On the basis of the variation of absorption at 507 nm and 600 nm (Fig. 2c and d), the binding constants $(K_1, K_2, K_3)^{11}$ and sensitivity¹² to H₂O are evaluated by a fitting method and are summarized in Table 1. As a result, it was found that OxP 5 substituted with hydrophilic carboxylate groups possesses the highest K_1 and sensitivity to H₂O. It is likely that carboxylate groups attract water molecules increasing their availability in the vicinity of OxP or that carboxylate moieties stabilize the H₂O-bound state of OxP. Differences in H₂O sensitivity arising from variation of N-substitution is a unique feature since it implies possible improvements in peformance by synthesis of more H₂O-sensitive OxPs. Importantly, OxP 5 is responsive to 37 ppm H₂O in THF (Fig. 2b, inset), so that it is technically possible to distinguish between freshly-purchased anhydrous THF $(H_2O < 50 \text{ ppm})^{13}$ and older wet THF ($H_2O > 50 \text{ ppm}$) simply by recording a UV-Vis spectrum of a solution of OxP of known concentration (which can be determined from the isosbestic point at 535 nm). Moreover, a map of calibration curves for OxP 5 can be constructed and used for fast determination of water concentration over a broad range (see ESI[†]). In addition, it should be noted that OxP is reusable (see ESI[†]), and that H₂O-sensitivity of OxP 5 is hardly affected by the inhibitor, 2,6-di-tert-butyl-4cresol (BHT, 600 ppm).¹³

¹H-NMR spectra of OxP **2** in THF- d_8 suggest that OxP binds H₂O molecules both at pyrrolic NH and at quinonoid C=O.

Table 1 Binding constants^{*a*} (K_1 , K_2 , and K_3) and sensitivities of OxPs 1-6 to H₂O in THF

Compound	K_{1}/M^{-1}	K_2/M^{-1}	K_{3}/M^{-1}	Sensitivity UV-Vis $(10^{-3} \text{ a.u. per ppm})$
1 2	$10.3 (\pm 2.1)^c$ 22.9 (±4.6)	2.36 0.42	0.00	$0.050 (\pm 0.005)$ 0.024 (±0.006)
3	$16.4 (\pm 3.3)^c$ 26.9 (+5.4)	1.28	0.07	$0.024 (\pm 0.006)$ $0.032 (\pm 0.006)$ $0.049 (\pm 0.016)$
5 5 + BHT ^b	$\begin{array}{c} 20.9 (\pm 3.4) \\ 89.8 (\pm 13.5) \\ 42.0 (\pm 8.4) \\ \end{array}$	5.53 1.49	0.01 0.14	$\begin{array}{c} 0.049 \ (\pm 0.010) \\ 0.102 \ (\pm 0.003) \\ 0.087 \ (\pm 0.009) \end{array}$
6	$69.0 \ (\pm 55.2)^{a}$	0.00	0.00	$0.003 (\pm 0.003)$

^{*a*} Binding constants (K_1 , K_2 , and K_3) are determined by the curve fitting method from Abs. at 507 nm and 600 nm. Binding models are shown in ESI. ^b 2,6-Di-tert-butyl-4-cresol (BHT, 600 ppm) was added. ^c Determined only from Abs. at 600 nm. ^d Compound 6 generally shows only a weak response to the presence of water (see ESI).

The peak at 9.8 ppm due to pyrrolic NH protons shifts downfield as H₂O is added (Fig. 3a), indicating occurrence of hydrogen bonding between pyrrolic NH and H₂O. Concurrently, ¹H-NMR peaks of tert-butyl groups at around 1.3 ppm become further divided (Fig. 3c). Since tert-butyl groups cannot form hydrogen bonds with H₂O, it appears that C=O groups close to the tertbutyl groups interact with H2O molecules similar to the case of unsubstituted OxP in the solid state.¹⁴ Also, ¹H-NMR peaks at around 6.6-7.7 ppm corresponding to pyrrole β-H and hemiquinonoid methine-H undergo downfield or upfield shifts (Fig. 3b) suggesting that binding of H₂O molecules at pyrrolic NH and quinonoid C=O causes changes in the π -electronic conjugation of OxP. Consequently, the absorption spectrum (*i.e.*, colour) of OxP should be changed. Binding of H₂O molecules at pyrrolic NH as well as quinonoid C=O is also supported by some X-ray crystal structures of OxPs.^{9,14}

Optical properties of OxP were investigated using timedependent density functional theory (TD-DFT).^{15,16} These calculations were applied in order to estimate at which position (*i.e.*, NH or C=O) interactions with water have a greater impact on the variations in the absorption spectra of OxP. As shown in Fig. 4(a), OxP 2 binds one H_2O molecule at pyrrolic NH and up to four H₂O molecules at quinonoid C=O. The interaction energy of H₂O with OxP implies that the NH position ($E = -68 \text{ kJ mol}^{-1}$) is more energetically favourable than quinonoid C=O ($E = -20 \text{ kJ mol}^{-1}$ per H₂O molecule). However, binding of H₂O at NH and quinonoid groups is apparently neither competitive nor cooperative since the total



Fig. 3 ¹H-NMR spectra of OxP 2 in THF- d_8 ([2] = 7.0 × 10⁻⁴ M) showing (a) pyrrolic NH region, (b) β-pyrrole and quinonoid moiety peaks, and (c) tert-butyl peaks. Assignments of peaks obtained by COSY and NOESY are shown in Fig. 1 (* indicates solvent impurity).



Fig. 4 (a) Top and side views of calculated hydrogen bonded structures of H₂O-bound OxP **2** based on DFT calculations (M06-L/6-31G(d,p), at 0 K in vacuum). Bromine atoms at benzyl substituents were replaced with hydrogen atoms to simplify calculations. Total binding energies of H₂O molecules are shown as E (kJ mol⁻¹). (b) Calculated absorption spectra of H₂O-bound OxP **2** based on DFT calculations (TD-M06-2x/6-31++G(d,p)).

interaction energy of five H₂O molecules (bound to both NH and C=O) ($E = -148 \text{ kJ mol}^{-1}$) is similar to the accumulated energy of each binding. Calculated absorption spectra of OxP **2** (Fig. 4b) suggest that binding of H₂O to pyrrolic NH does not affect the absorption spectrum of OxP **2**. On the other hand, binding of H₂O molecules to quinonoid C=O shifts slightly the absorption maximum of OxP to longer wavelength, which partly explains the enhancement of absorption at 600 nm as depicted in Fig. 2(b).

In conclusion, we have demonstrated that traces of H_2O (~50 ppm) in THF are detectable by means of UV-Vis spectroscopy using OxP derivatives as a probe. This makes a rapid and convenient method for analysing supposedly anhydrous THF prior to mixing with water-sensitive reagents towards improving laboratory safety and reaction yields. We are currently attempting to better understand the mechanism of water sensing. OxP may also be applicable to other binary solvent systems including water, and improvement of H_2O sensitivity by varying N,N'-substitution may be possible.

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