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Turning optical chemosensors into optodes: a quantum chemical and experimental case-study

Tommaso Carofiglio,* Roberto Fornasier, Carlo Fregonese, Alberto Gambalunga, Giacomo Saielli and Umberto Tonellato

Istituto CNR per la Tecnologia delle Membrane (Sezione di Padova), Dipartimento di Scienze Chimiche, Università di Padova, Via Marzolo 1, 35131 Padova, Italy

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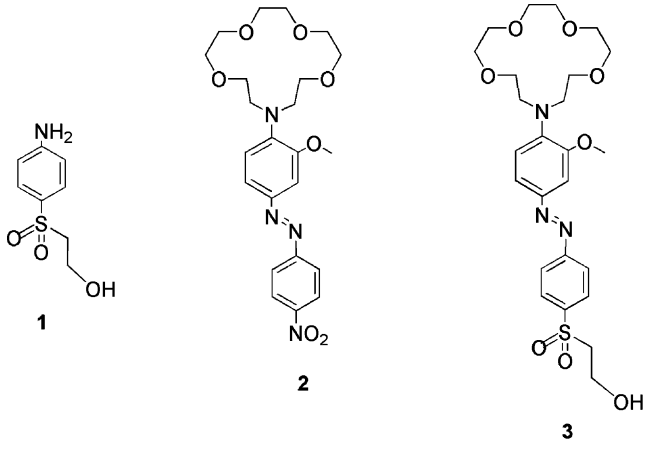
Abstract—Replacing a nitro-group with a 2-hydroxyethyl sulfonyl moiety in an optical sensor for sodium ions allowed for its covalent linking into cellulose membranes. Both quantum chemical and experimental data confirmed the low impact of such structural modification on the sensor performances, thus representing a quite general way for building optodes.

Chemical sensors arrays have emerged as a powerful alternative to chromatography-based methods of analysis for multianalyte determinations.[1] The approach of using sensor arrays for chemical analysis mimics the organization and functioning of the mammalian olfactory and gustatory senses. In these systems, odorant and tastant molecules are identified through a composite response obtained from a set of receptors with low specificity.[2] The development of sensor arrays possessing a broadband sensing capability is a crucial issue in many fields such as medical diagnostic, environmental analysis and industrial process monitoring. To this purpose, the individual sensors should not be highly selective. On the contrary, they must cover an ample gamut of physicochemical interactions and provide partially correlated responses.

Recently, we have developed a simple methodology for the multiparallel synthesis of pH and transition-metal sensitive azo-dyes and for their covalent arraying onto cellulose membranes.[3] The syntheses of the dyes and the immobilization chemistries were carried out in parallel, in microscale amount, in one-pot fashion. In addition, purification or isolation steps were not required. More in detail, our method exploited the 2-(4-aminophenylsulfonyl) ethanol, **1** (Scheme 1), which has been previously used as a key-component for the production of nonleaching pH-sensors supported onto cellulose acetate overhead transparencies[4] and polyvinyl alcohol based materials.[5] The usefulness of compound **1** comes from its hetero-bifunctional nature. Indeed, the aniline group allows for the synthesis of an azo-chromophore via diazotization followed by coupling with aromatic amines or phenols. On the other hand, the 2-hydroxyethyl sulfonyl moiety, a precursor of the cellulose-reactive vinylsulfone group, provides a handle for the covalent attachment of the dye onto cellulose membranes or other supports bearing nucleophilic hydroxyls.



Scheme 1.

Several chromogenic azo-dyes are presently available for chemical sensing analytes such as monosaccharides,[6]

* Corresponding author. E-mail: tommaso.carofiglio@unipd.it

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fluoride,[7] cyanide[8] or other anions,[9] transition metals and alkaline ions.[10] The mechanism adopted by these systems for translating the receptor–analyte association into a colour variation is principally one: a perturbation, upon complexation, of an internal charge-transfer (ICT) process between an acceptor–donor chromophore pair. The electron-rich group (donor) is usually integrated into the receptor, to maximize sensor sensitivity. Its chemical nature depends on the recognition process evoked by the sensor. The electron-deficient group (acceptor) of choice is most typically a *p*-nitrophenyl substituent, probably for synthetical convenience and good chemical stability. We reasoned that replacing such nitro-group with the 2-hydroxyethyl sulfonyl moiety could represent a quite general and straightforward way for turning these chemosensors into optodes.

As a proof-of-principle, we took as a reference the optical sensor **2** (Scheme 1), an established analytical tool for detection of sodium ions in aqueous solution previously reported by Gunnlaugsson et al.[10] In particular, our research had two main objectives: (1) to estimate, by quantum chemical calculations, the impact of replacing the nitro group in **2** with the 2-hydroxyethyl sulfonyl moiety, and (2) to synthesize compound **3**[†] (Scheme 1), a cellulose-linkable analogue of **2** and to verify its sensing properties as a free and surface bound species.

Quantum chemical calculations for compounds **2** and **3** have been carried out at the DFT level.[11–16] Details about compounds **2** and **3** calculations are reported in Supplementary data. The optimized structures for compound **3** and its Na^+ complex are reported in Figure 1.

Next, we calculated the binding affinities of compounds **2** and **3** for Na^+. The two energies were very close (−92.6 kcal/mol for **2**·Na^+, and −93.8 kcal/mol for **3**·Na^+). These calculations were carried out in vacuo and, therefore, calculated energies are not a good estimate for the experimental data in solution. Nevertheless, the fact that both compounds interact similarly with Na^+ indicates that the effect of replacing the nitro group with the 2-hydroxyethyl sulfonyl group is expected to be negligible.

Scheme 2 depicts the synthetic procedure we followed in this work. Compound **3** was prepared according to a synthetic route described by Wolfbeis and co-workers.[4] Aza-crown **4** was synthesized starting from 2-methoxyaniline through a three step procedure reported in the literature.[10] For the synthesis of compound **3**,[17] the hetero-bifunctional scaffold **1** was first diazotized with sodium nitrite in concentrated HCl at 0 °C. Then, the diazonium salt of **1** was coupled with **4** to form the corresponding azo-dye. Column chromatography on basic alumina (eluent ethyl acetate–methanol = 94:6) led to the isolation of compound **3** in 26% yield. The identity

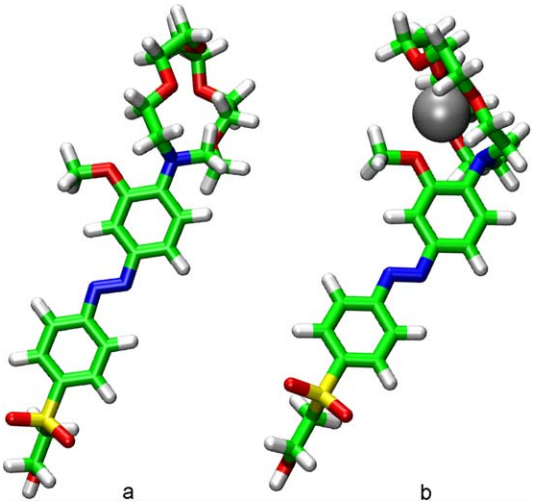
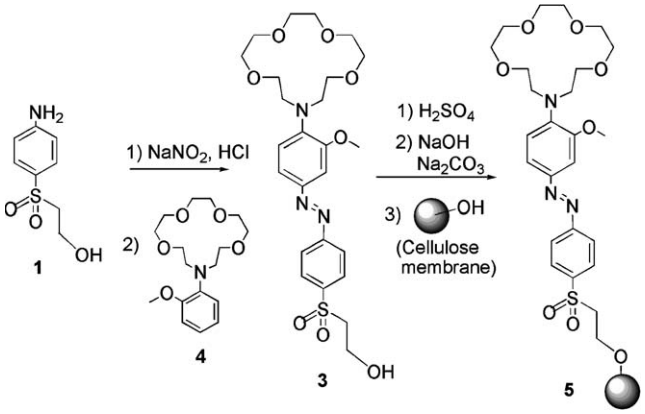


Figure 1. Optimized structures for compound **3** (a) and **3**·Na^+ (b).



Scheme 2.

of **3** was confirmed by ^1H NMR and ESI-MS.[17] Dye activation and cellulose dyeing were carried out by esterification of **3** with concentrated H_2SO_4 followed by raising the pH above 10 (to produce the cellulose reactive vinyl sulfone group) in the presence of the pre-hydrolyzed cellulose acetate membrane.[18]

Azo-dyes **3** and **5** are pH sensitive due to the protonation of the azo-crown amino group. The acid–base behaviour of **5** has been conveniently studied by UV–vis spectrophotometric titration. To this aim, a sample of dye-functionalized membrane was taped inside a disposable plastic cuvette using a bi-adhesive tape. This tape was not transparent at $\lambda \leqslant 350$ nm, thus precluding the acquisition of the UV–vis spectrum of the acidic form of the dye ($\lambda_{max} = 343$ nm). Upon raising the pH from 2 to 12, the band corresponding to the basic (neutral) form of the dye ($\lambda_{max} = 468$ nm) markedly increased (Fig. 2) with the formation of an isosbestic point at 365 nm. Fitting the titration data with a sigmoid function, a pK_a value of 3.0 was obtained.

For a comparison purpose, also the acid–base behaviour of **3** was studied in solution. The acidic forms of **3** showed an absorption maximum at 312 nm, which reduced in intensity upon increasing the pH with forma-

[†] As pointed out by one of the Referees, compound **3** is similar to a compound previously described by Dix and Vogtle,[19] which was a diazobenzene substituted by a crown ether and a SO_2OH group. However, the analogy is only formal since Vogtle's derivative is not suitable for cellulose covalent linking.

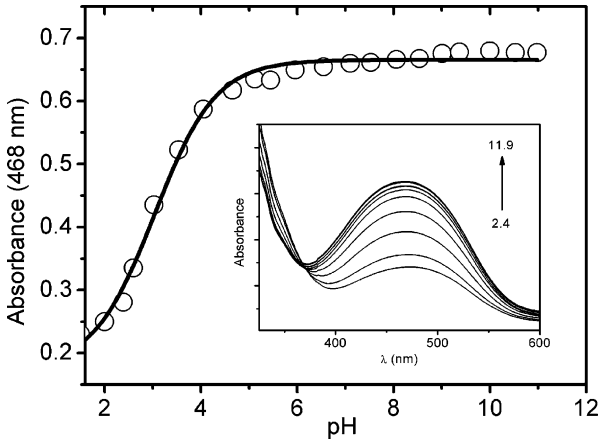


Figure 2. Absorption of **5** at 468 nm versus pH. Inset: UV–vis spectra recorded during the titration.

tion of a new band at 460 nm and two isosbestic points at 282 and 365 nm. On the basis of pH titration plot obtained from the absorption data, the pK_a of **3** was found to be 3.8. The latter value compares well with the one found for **2** (p$K_a = 3.9$).[10] It should be noted that the difference in the acidity constant between **3** and **5**, which has been already observed in similar systems, can be likely ascribed to the micro-environmental conditions exerted by the dye inside cellulose polymeric network.[4]

On the basis of the acid–base behaviour of compounds **3** and **5**, the Na^+ sensing of these receptors was studied at pH = 7, that is, in the pH-independent region of the dye. By the way, this pH is ideally suited for using optical sensor **5** under physiological conditions. The binding with sodium was studied in water–methanol (1:1 v/v), Tris buffer, and in the presence of 0.05 M tetramethylammonium chloride to keep the ionic strength constant. Titration of **3** with Na^+ ions allowed the determination of a formation constant of 7.2 M^{-1}, which is similar to that reported for **2** in the same conditions (17.8 M^{-1}).[10] This result substantially corroborates our theoretical calculations. Most importantly, receptor **3** is able to bind sodium ions also when covalently attached onto the cellulose membrane. Figure 3 shows how the UV–vis

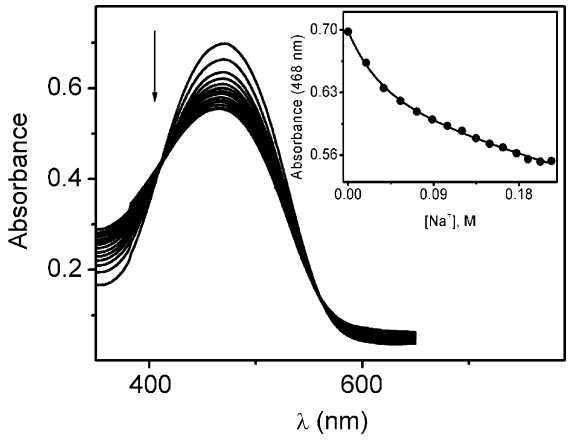


Figure 3. Changes of the UV–vis spectrum of **5** upon exposing the membrane to sodium ion solutions of increasing concentrations (0–220 mM). Inset: titration plot of **5** with sodium ions.

spectrum of **5** changed upon exposing the membrane to solutions of sodium ions at different concentrations. The inset reports the corresponding titration plot.

In conclusion, we have demonstrated that a 2-hydroxyethyl sulfonyl moiety can be used instead of a nitro group for the construction of a cellulose-linkable sodium sensor. Importantly, the generality of this approach holds promise for application to other azo-dye chemosensors based on push–pull chromophoric systems. Work towards this end continues in our laboratory.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.026.

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11. Computational details: geometry optimizations have been run at the DFT B3LYP/6-31G** level of theory[12,13] with the Gaussian 03 software package.[14] Excited state calculations have been run both at the semi-empirical level (ZINDO/S),[15] including the 40 highest occupied orbitals and the 40 lowest virtual orbitals, and at the ab initio level CIS/6-31G**.[16]

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17. Synthesis of compound **3**: compound **1** (72.8 mg, 0.31 mmol) was dissolved in 0.6 M HCl (1.0 mL) and cooled down at 0 °C. A solution of $NaNO_2$ (21.2 mg, 0.31 mmol) in water (1.0 mL) was then added dropwise. After 15 min the above solution was added dropwise to a solution of azacrown **2** (100 mg, 0.31 mmol) in THF/H_2O 1:1. The colour of the solution turned purple red. The reaction mixture was allowed to reach room temperature and was then stirred overnight. The solution was concentrated and the pH adjusted to 8 with concentrated NH_4OH causing the formation of a dark red solid. Extraction with chloroform (5 mL, three times) and drying over $MgSO_4$ led, after evaporation, to a red oil. Purification was carried out by preparative column chromatography (basic alumina, activated I, eluent: ethyl acetate–methanol = 94:6) obtaining compound **3** as a red oil (43 mg, 26%). UV–vis (acidic form, HCl 0.1 M, $\lambda_{max} = 312$ nm, basic form as K^+ complex, KOH 0.1 M, $\lambda_{max} = 421$ nm). ^1H NMR ($CDCl_3$, δ): 7.4–8.2 (m, aromatic protons, 7H), 3.3–4.1 (m, aliphatic protons, 27H). ESI-MS (methanol): 538.3 ([**3**−H]$^+$, calculated 538.63), 560.2 ([**3**−Na]$^+$, calculated 560.2).
18. Cellulose acetate dyeing: compound **3** (7.6 mg, 0.014 mmol) was dissolved in concentrated sulfuric acid (200 μL). After 30 min the solution was diluted with cold water (2.0 mL), then the pH was increased to 10 by adding a 8 M aqueous solution of NaOH (about 1 mL). This led to the formation of the cellulose-reactive vinyl-sulfone form of **3**. The solution was applied to pre-hydrolyzed cellulose acetate membranes (0.1 M NaOH for 30 min) by using the previously reported eight-spot Teflon reactor.[3] Dying was performed at room temperature for 8 h. The membrane was washed with water, 0.1 M HCl and water again in order to remove reactants and some absorbed dye.
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