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# Chromophoric Barbituric Acid Derivatives with Adjustable Hydrogen-Bonding Patterns as Component for Supramolecular Structures

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**Summary:** The barbituric acid moiety of the presented dyes shows multifunctional properties like acidochromism, solvatochromism, and adjustable hydrogen-bonding pattern for molecular recognition. Hydrogen-bonding ability, acidity and solvatochromic effects are studied for a series of *N*-alkyl substituted 5-(4-nitrophenyl)-barbiturates. Solvatochromism and metal ion complexation are also investigated using chromophoric thiobarbituric acid derivatives.

**Keywords:** barbiturates; dyes/pigments; molecular recognition; solvent effects; transition metal complexes

## Introduction

Barbituric acids belong to the family of 2,4-pyrimidione derivatives which play an important role in nature and in technical or pharmaceutical application.[1–3] The versatility of the barbituric acid moiety is attributed to its possibility to serve alternatively as donor or as acceptor substituent depending on the binding mode to a π-electron system. The different mesomeric effects of the barbiturate can be especially utilised for the construction of chromophoric chemosensors. This behaviour can be easily demonstrated by its incorporation in various types of chromophores as shown in Figure 1.

Merocyanine dyes which contain the barbituric acid moiety as a (–)M-substituent are well established, because their synthesis is readily feasible by an aldol condensation of barbituric acid or its *N*-substituted derivatives with aromatic aldehydes.[4,5] Furthermore, Oxonol dyes, like Murexid are well known indicators for the detection of cyanide and metal ions, respectively.[6,7] These dyes are push-pull electron systems where the two opposite electronic effects of the barbituric acid are directly combined. Surprisingly, chromophores with barbituric acid as an electron donor substituent are still not established. Dilituric acid (5-nitrobarbituric acid) may serve as a known derivative, but it is not really an applicable chromophore.[8,9] Furthermore, this barbiturate shows an ADA and a DDA hydrogen-bonding pattern (D: hydrogen bond donor, A: hydrogen bond acceptor).

To demonstrate the applicability of the barbituric acid as a versatile substituent in chromophoric π-electron systems, four novel types of dyes (Figure 2) within the barbituric acid family are presented in this mini-review.

The motivation of the study using barbituric acid as a changeable substituent is borrowed from three different research topics:

- presence of hydrogen-bonding sequences similar to nucleic acid bases[2,4]
- adjustable electrophilicity and nucleophilicity of the substitutent at the C5 carbon of the barbituric acid[10]
- solvatochromic properties[5,11–13,20]

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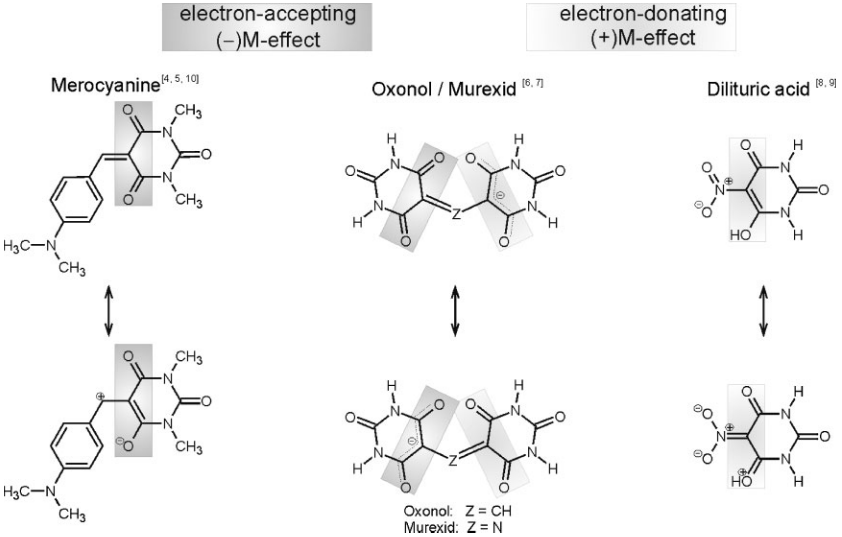


*Figure 1.*
Mesomeric effects of different barbituric acid derivatives.

To achieve this target, we present four different molecular structures (Figure 2) which have been reported by us previously.[11–16] Each dye from Figure 2 has specific advantages and restrictions.

## Results

### SCHIFF Bases

The SCHIFF bases derived from 5-aminobarbituric acid are highly multifunctional, because their different sites tailor the molecular properties as shown in Figure 3.[11,14] Compound **SB3** ($X = O$, $R = n\text{-}C_4H_9$ and $R^1 = NO_2$) is evidently solvatochromic and forms a stable hydrogen-bonded complex with 2,6-diacetamidopyridine **DAC**, which can be readily examined by means of UV/Vis spectroscopy.[11] Unfortunately, all SCHIFF bases are rather unstable in protic solvents, especially when the supramolecular complex formation with stronger bases is investigated. Therefore, its application is restricted to non-protic solvents.

### Enolisable 5-(4-nitrophenyl)-Barbituric Acids

Alternatively, we search for related compounds where no hydrolysable groups are present. 5-(4-Nitrophenyl)-barbituric acid derivatives are suitable for this purpose. In spite of its simple seeming molecular structure, this type of dyes was still unknown.

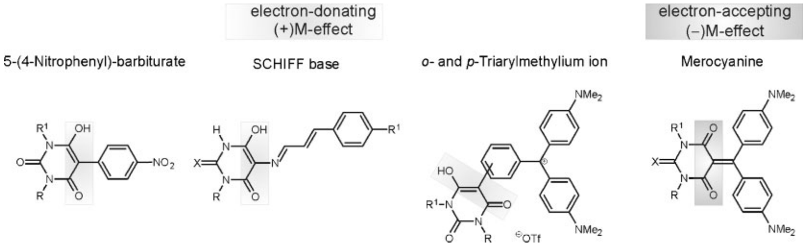


*Figure 2.*
Novel solvatochromic barbiturates with multifunctionality.

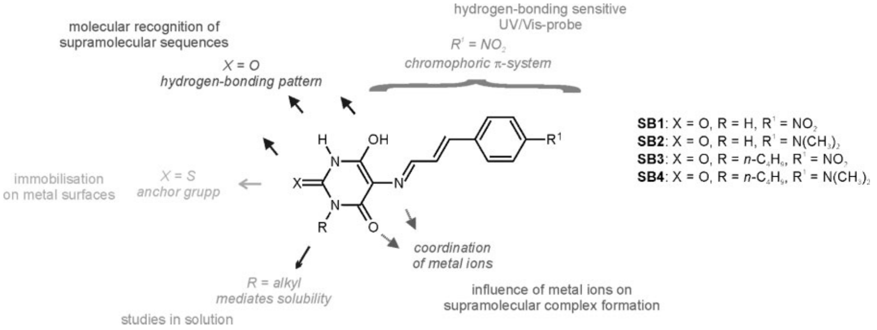


***Figure 3.***
Solvatochromic SCHIFF bases available from 5-aminobarbituric acid derivatives and cinamaldehydes and indication of its molecular functions.[11,14].

These enolisable barbiturates with different NH-substitution undergo a variety of equilibriums (Figure 4) which complicate the interpretation of solvatochromic effects. Molecular aspects of the structure in the solid-state are studied in detail which allows an interpretation of the observed UV/Vis effects.[15] The applicability of enolisable barbiturates as UV/Vis probes is shown by the solvatochromism of a series of 5-(4-nitrophenyl)-barbituric acids.

The position of the visible UV/Vis absorption band of those compounds is strongly dependent on the polarity of the solvent as shown exemplary in Figure 5 and Table 1 for the *N*-methyl-substituted 5-(4-nitro-phenyl)-barbituric acid **NiMe**. The switching between the two principle tautomeric forms is associated with dramatic changes in the extent of π-conjugation. The enol-substituted barbituric acid moiety contributes to a push-pull system due to the *para* conjugation with the nitro group which originates the solvatochromic properties.

The Kamlet-Taft solvent parameters have been established for studying solvent effects on UV/Vis spectra.[17,18] The Kamlet-Taft equation, in its simple form, is:

$$(\mathrm{XYZ}) = (\mathrm{XYZ})_o + \mathrm{a}\alpha + \mathrm{b}\beta + \mathrm{s}\pi^* \qquad (1)$$

(XYZ) is the result of a solvent-dependent process; $(\mathrm{XYZ})_o$ is the value of a reference system, for example the gas phase or a non-polar solvent. $\alpha$ describes the hydrogen bond acidity, $\beta$ describes the hydrogen bond basicity and $\pi^*$ the dipolarity/polarisability of the solvent. a, b, and s are the solvent-independent correlation coefficients reflecting the proportions of the respective parameters

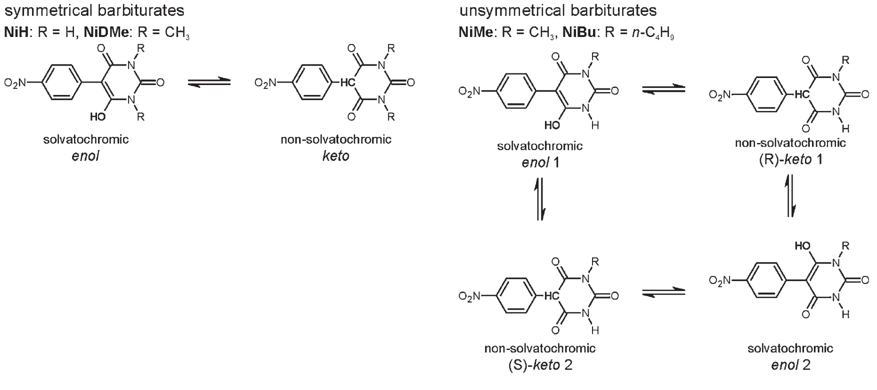


***Figure 4.***
Tautomeric equilibriums of 5-(4-nitrophenyl)-barbituric acid derivatives.

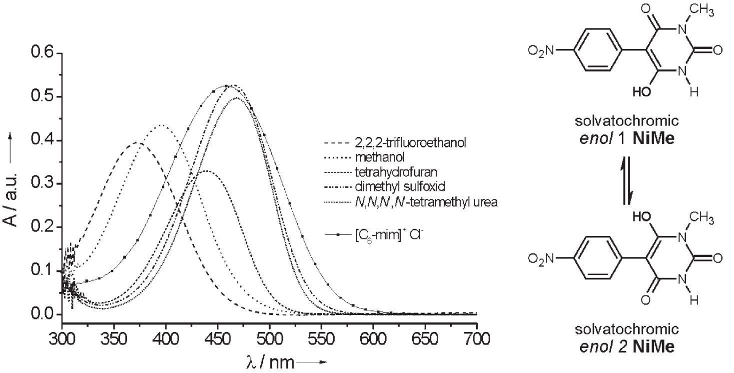


***Figure 5.***
UV/Vis spectra of 1-methyl-5-(4-nitrophenyl)-barbituric acid **NiMe** measured in five organic solvents and one room temperature ionic liquid.

on the result (XYZ) of the chemical process. The accuracy of the correlation equation is determined by the number of solvents used (n), the correlation coefficient (r), the standard derivation (sd) and the significance (f).

For the correlations a set of data derived from more than 20 various solvents have been taken into account.[19] The results of the multiple square correlation analyses according to Equation 1 are shown in Table 2. In comparison with the small magnitude of the conjugated system, the solvatochromic ranges detemined ($\Delta\tilde{\nu} = -5252$ to $-5792$) are enourmously large and indicate a pronounced push-pull system of 5-(4-nitrophenyl)-barbituric acids. Each of the solvent polarity coefficients ($\alpha$, $\beta$ and $\pi^*$) has an effect on the position of UV/Vis absorption band of the enol-substituted barbiturates.

Notably, a strong bathochromic shift is observed in solvents with high $\beta$-value (like TMU and DMSO, Table 1). This is a clear proof for the presence of the barbiturate in its enol form which is evidently stabilised by hydrogen bonds between the proton of the enol-oxygen and the solvent. However, alkyl

***Table 1.***
UV/Vis-Absorption maxima ($\tilde{\nu}_{max}$) of the four 5-(4-nitrophenyl)-barbiturates in representative solvents and ionic liquids, the empirical polarity parameters $\alpha$, $\beta$, $\pi^*$ and the calculated solvatochromic range.[12,17–19]

| Solvent | $\alpha$ | $\beta$ | $\pi^*$ | $\tilde{\nu}_{max}$ [$10^{-3}$ cm$^{-1}$] | | | |
|---|---|---|---|---|---|---|---|
| | | | | **NiH** | **NiMe** | **NiBu** | **NiDMe** |
| Tetrahydrofuran | 0.00 | 0.55 | 0.58 | – | 22.71 | 23.05 | 22.77 |
| Pyridine | 0.00 | 0.64 | 0.87 | 21.34[d] | 21.41 | 21.33 | 21.34[d] |
| Dichloromethane | 0.13 | 0.10 | 0.82 | – | 23.39 | 22.81 | 23.86 |
| TMU[a] | 0.00 | 0.80 | 0.83 | 21.34[d] | 21.33[d] | 21.30[d] | 21.39 |
| DMSO[b] | 0.00 | 0.76 | 1.00 | 21.39 | 21.44 | 21.50 | 21.58 |
| Methanol | 0.98 | 0.66 | 0.60 | 25.26 | 25.27 | 25.14 | 25.12 |
| Formamide | 0.71 | 0.48 | 0.97 | 23.98 | 23.76 | 23.67 | 23.50 |
| TFE[c] | 1.51 | 0.00 | 0.73 | 27.13[e] | 26.80[e] | 26.54[e] | 26.90[e] |
| $[C_6\text{-mim}]^+$ $BF_4^-$ | 0.44 | 0.60 | 0.96 | 22.77 | 22.52 | 22.55 | 22.24 |
| $[C_6\text{-mim}]^+$ $Br^-$ | 0.35 | 0.88 | 1.06 | 21.88 | 21.97 | 21.88 | 21.83 |
| $[C_6\text{-mim}]^+$ $Cl^-$ | 0.30 | 0.97 | 1.06 | 21.68 | 21.76 | 21.58 | 21.83 |
| $\Delta\lambda$ [nm] | | | | 100 | 96 | 93 | 97 |
| $\Delta\tilde{\nu}$ [cm$^{-1}$] | | | | −5792 | −5470 | −5232 | −5562 |

[a]Tetramethyl urea, [b]Dimethyl sulfoxide, [c]2,2,2-Trifluorethanol, [d]Largest bathochromic shift, [e]Largest hypsochromic shift.

***Table 2.***
Results of the multiple correlation analysis of the solvatochromic compounds **NiH**, **NiMe**, **NiBu** and **NiDMe** using the Kamlet–Taft linear solvation energy relationship.[19]

| compound | $\tilde{\nu}_{max,\,o}$ | a | b | s | r | sd | f | n |
|---|---|---|---|---|---|---|---|---|
| **NiH** | 24.98 | +2.85 | −1.27 | −1.93 | 0.980 | 0.350 | <0.0001 | 20 |
| **NiMe** | 25.60 | +2.50 | −2.09 | −2.17 | 0.955 | 0.460 | <0.0001 | 25 |
| **NiBu** | 26.08 | +2.30 | −1.91 | −3.42 | 0.934 | 0.545 | <0.0001 | 27 |
| **NiDMe** | 24.97 | +2.53 | −2.03 | −2.16 | 0.945 | 0.473 | <0.0001 | 27 |

substitution of the barbituric acid at the two nitrogen atoms does not significantly alter the solvatochromic character of the 5-(4-nitrophenyl)-barbiturates. The determined correlation coefficients a, b and s are in the same order of magnitude in the set of **NiH** (no NH-substitution) to **NiMe**/**NiBu** (one *N*-alkyl group) to **NiDMe** (two *N*-methyl functions). Especially compound **NiDMe** demonstrates that the influence of the *β*-term is caused mainly by the enol hydrogen - solvent interaction.

In order to study the effects of supramolecular complex formation on the UV/Vis shift we use **NiBu** because of its good solubility and the presence of solely one hydrogen-bonding sequence which allows a straightforward interpretation. The results of the complex formation with nucleic acid bases and related model compounds are shown in Figure 6. The question was: Is it possible to differentiate between different kinds of multiple hydrogen-bonding sequences with the adjustable chromophore **NiBu** by UV/Vis spectroscopy?

Although the UV/Vis shifts are not dramatic compared to solvatochromic effects, the adaption of the barbituric acid derivative to various hydrogen-bonding patterns has been clearly demonstrated (Figure 7). Therefore, the concept to use enolisable chromophoric barbiturates bearing the barbituric acid moity as a (+)M-substituent is promising to construct new classes of dyes for molecular recognition in future application.

### Carbenium Ions

Another interesting type of barbituric acid dyes contains an electrophilic centre as exemplified in Figure 8 and 9. There, the barbiturate moiety with its particular hydrogen-bonding pattern serves as an electron-accepting group. The strong electron-donating effect of two dimethylaminophenyl rings results in a highly polar push-pull system.[13,16]

5-Phenylbarbituric acids react with triflic anhydride-activated benzophenones to yield an O-alkylated intermediate which

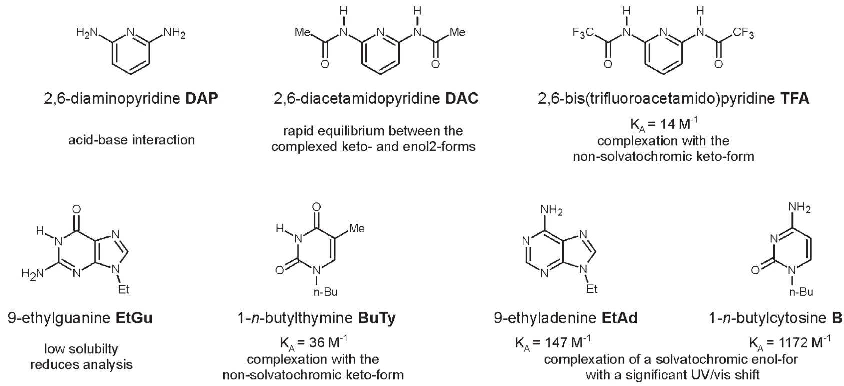


***Figure 6.***
Investigated receptors to interact with the enolisable barbiturate **NiBu** by means of supramolecular complex formation according to Figure 7.

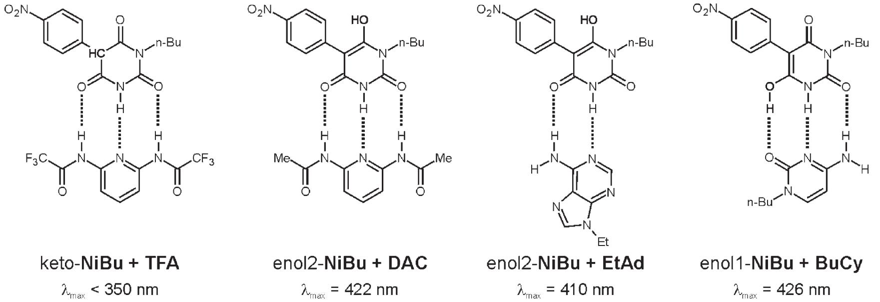


***Figure 7.***
Representative supramolecular complexes of NiBu with artificial receptors as evidenced to recognize different hydrogen-bonding patterns by UV/Vis spectroscopy.

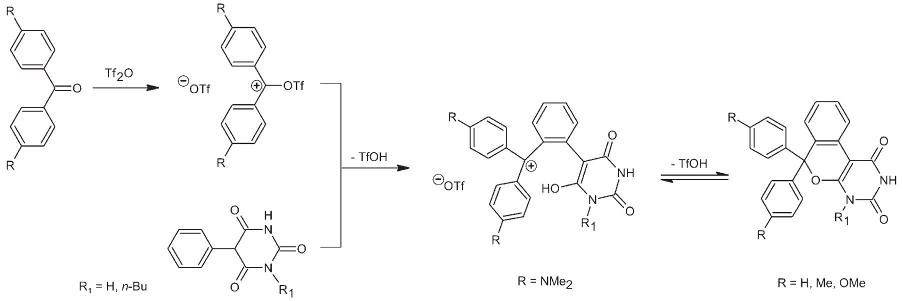
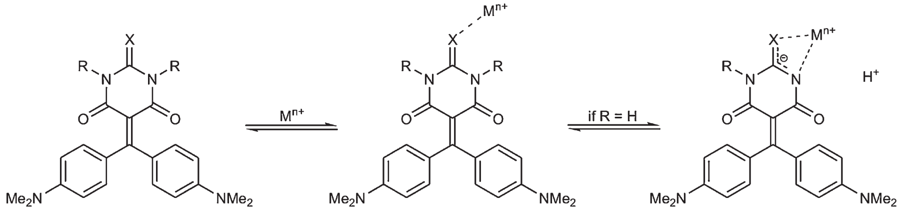


***Figure 8.***
Synthesis of cationic barbiturates and their intramolecular recombination equilibrium.



| | X | R |
|---|---|---|
| MC-O-Me | O | Me |
| MC-S-Et | S | Et |

| | X | R |
|---|---|---|
| MC-O-H | O | H |
| MC-S-H | S | H |

***Figure 9.***
Examined merocyanine-like dyes and their possible interaction with metal ions.

rearranges to an *ortho*-substituted carbeniumion. Depending on the electrophilicity of the cationic centre, an intramolecular nucleophilic attack of the barbiturate enol may then occur to give cyclic enol ethers as shown in Figure 8.[16] This ring closure proceeds very regioselectively, so that in any case the ADA hydrogen-bonding pattern is preserved and stable complexes with the receptor **DAC** are obtainable. On the other hand, the highly stabilised Malachite Green derivatives can be isolated as salts which are, however, only slightly solvatochromic.

## Merocyanine Dyes

The merocyanine-like compounds **MC** (Figure 9) should be readily available by

*Table 3.*
Results of the multiple correlation analysis of the solvatochromic merocyanine dyes using the Kamlet–Taft linear solvation energy relationship.[19]

| compound | $\tilde{\nu}_{max,0}$ | a | b | s | r | sd | f | n |
|---|---|---|---|---|---|---|---|---|
| **MC-O-H** | 20.94 | −1.62 | +0.84 | −2.21 | 0.97 | 0.23 | <0.0001 | 22 |
| **MC-O-Me** | 21.12 | −1.58 | – | −2.05 | 0.98 | 0.20 | <0.0001 | 13 |
| **MC-S-H** | 19.73 | −1.26 | +0.49 | −1.81 | 0.96 | 0.21 | <0.0001 | 23 |
| **MC-S-Et** | 19.65 | −1.06 | – | −1.84 | 0.98 | 0.15 | <0.0001 | 26 |

an aldol condensation of substituted benzophenones with barbituric acid or its *N*-substituted derivatives as shown by Rezende *et al*. for the solvatochromic dye **MC-O-Me** synthesized from Michler's Ketone and *N*,*N*′-dimethylbarbituric acid.[20]

Similar dyes with free NH-groups are, however, hardly described which can be explained by the fact that simple aldol condensation of barbituric acid with benzophenones give only low yields of the target products. Instead, a mixture of N-, O- and C-substituted barbiturates is obtained under different conditions which is objective of deeper mechanistic studies.[21] Finally, the synthesis was successfully accomplished by using a two step synthesis starting from Michler's Hydrol Blue.[13] Of particular interest are barbituric acid derivatives which possess both an electrophilic carbon atom and acidic protons at the oxygen and/or nitrogen atoms of the barbiturate moiety. Here, an attacking nucleophile can interact alternatively with the carbon atom or the OH or NH functions. The NH group plays also a role when the complex formation with metal ions is investigated due to its potential tautomerism (Figure 8).[22]

To gain insight into the interaction of the different sites with the surrounding, solvatochromic studies according to Equation 1 have been carried out, the results of which are summarised in Table 3.[13]

The influence of the dipolarity/polarisability is of the same order of magnitude as for the nitrophenylbarbituric acids. In contrast, the coefficients describing the hydrogen-bonding ability, $\alpha$ and $\beta$, have the opposite sign in the merocyanine-like dyes. This evidently indicates that the barbiturate moiety in these two types of dyes actually has opposite electronic effects, i.e. the barbiturate acts in the merocyanine as an electron-withdrawing substituent. It is also interesting to note that, in the merocyanine series, the solvatochromic properties are strongly influenced by the substitution pattern of the barbituric acid group both at the nitrogen atom as well as at the C2-(thio-)carbonyl group.

Metal ion complex formation should have similar effects compared to solvent effects when the ADA sequence of the barbituric acid is involved. It is well known that oxygen and sulphur atoms show a different complex forming ability towards metal ions. Therefore, we used both the oxo- and thio-derivative ($X = O$ or $X = S$ according to Figure 8) to examine whether metal ion complex formation has an effect on the UV/Vis absorption band.

It is noteworthy that the dialkylated derivative **MC-S-Et** does not show significant effects when treated with metal salts while the non-alkylated compounds generally show a bathochromic shift of the UV/Vis absorption maximum. Then again, the UV/Vis absorption shifts are larger for the thiobarbiturate **MC-S-H** than for the barbiturate **MC-O-H**. Figure 10a shows the UV/Vis spectra of **MC-S-H** when treated with various metal salts in acetonitrile. From UV/Vis titration of this compound with $ZnCl_2$ (Figure 10b) an association constant of $K_A = 75\,M^{-1}$ is calculated which is also higher compared to **MC-O-H** with $K_A = 33\,M^{-1}$. Due to the variable sensitivity towards metal ions, these dyes might eventually be suitable as chemosensors for distinguishing between several transition metals.

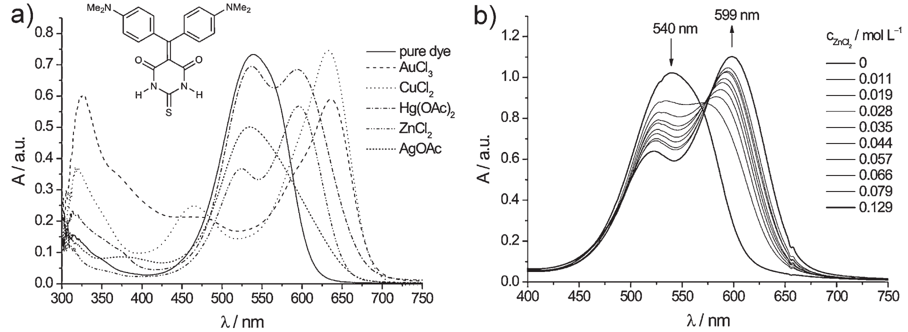


***Figure 10.***
UV/Vis spectra of **MC-S-H** in acetonitrile a) after adding various metal salts; b) with increasing amounts of $ZnCl_2$.

## Conclusions

In the present mini-review we describe the multifunctional properties of four novel types of chromophoric barbituric acid derivatives containing the barbituric acid moiety as an electron donating or electron accepting substituent. These dyes are suitable as chemosensors due to the variable sensitivity towards environmental polarity effects, complementary hydrogen-bonding patterns, and metal ions. This behavior is shown by several UV/Vis titration experiments.

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