JOC Note

Chiral 1,2- and 1,3-Diol-Functionalized Chromophores as Lego Building Blocks for Coupled Structures

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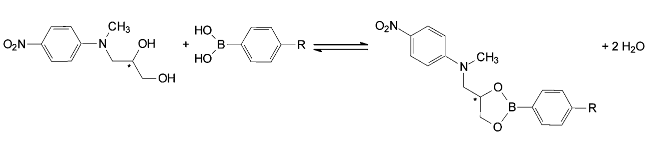

Chiral nitroanilines containing 1,2- or 1,3-diol functionalities have been synthesized by nucleophilic aromatic substitution of fluoronitroanilines with 1-aminopropane-2,3-diols and 2-aminopropane-1,3-diol in the melt. X-ray structure analyses confirm retention of the configuration of the chiral center. The novel chromophores are suitable to link reversibly to various substituted arylboronic acids which allows the construction of new solvatochromic sensor molecules suitable to response to solvent and anion coordination by fluoride. The solvatochromism of the new compounds has been studied using the Kamlet−Taft LSE relationship.

According to the definition supramolecular structures are built up as a result of noncovalent interactions between individual building blocks.[1−3] The principle of reversibility guarantees that the individual building blocks are assembled according to a plan and can be separated again as with Lego building blocks. In 1988, Michl and Stoddart developed, independently of one another, the idea of combining organic and/or inorganic molecules using a building plan, as with Lego.[4−6] However, there is still no successful synthetic concept of assembling molecular building blocks to form an unsymmetrical superstructure using a plan. An important disadvantage of many compounds whose formation is reversible is the thermal lability of the binding points, which also determines the average lifetime of the functional units.

To construct bifunctional probes, we looked for compounds with covalent binding points where both the principle of reversibility and also a high degree of robustness are guaranteed. For this it is necessary for the molecules on the periphery to be functionalized in such a way that they can be chemically bonded to and separated again from other functional molecules. We chose solvatochromic organic chromophores with 1,2- and 1,3-diol functions. Bonding with boronic-acid-based sensor molecules is of particular interest for developing bifunctional and adjustable chromophores.[7−13] Boronic-acid-containing organic compounds are becoming increasingly popular as macromolecular substrates in organic synthesis and combinatorial chemistry.[14,15]

By reaction with functionalized boronic acids 1,2- and 1,3-diols can be converted into boronate esters.[7−15] These can easily be cleaved using base-catalyzed hydrolysis. Besides this functionalization, this class of molecule has other uses:

(i) The chromophoric compounds can be obtained as (R)- or (S)-enantiomers or as racemic mixtures. This allows for easy integration of chiral information into the chromophore.

(ii) 1,2- and 1,3-diol functions can also be functionalized in other ways, for example, through the introduction of fatty acid chains. They can thus be used as solvatochromic components for chiral lipid layers for localized measurement of micropolarity.[16,17]

(iii) Solvatochromic chromophores give information on the polarity of the surroundings of the molecule (solvent, surface, micelles) through the measurement of the UV/vis absorption maximum.[18,19]

We chose nitroaniline derivatives for the preliminary investigations as these have been widely used in materials science (NLO)[20−22] and analysis (solvatochromism).[23−31] There are a large number of substituted *p*-nitroaniline

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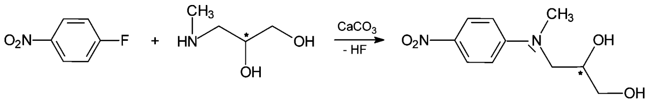
SCHEME 1. Nucleophilic Aromatic Substitution of Aminopropandiols with Activated Fluoronitrobenzenes, e.g., of Compound 1



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derivatives which are used as solvent-sensitive indicators for setting up polarity scales,[23–26] as lipophilic indicators in micelles, bilayers, and biological membranes,[27–31] or guests in cyclodextrine.[32]

The aim of the present work was to synthesize and structurally characterize a range of new hydrophilic nitroaniline derivatives and to investigate their solvatochromic properties in detail. In particular, we wanted to show whether and how the free 1,2- and 1,3-diol functions and those capped by reaction with various aromatic boronic acids have an effect on the chromophoric π-electron system as a result of interactions with the surroundings of the molecules and what proportion of these are dipole–dipole and/or hydrogen bond or acid–base interactions. Also, the effect of substituents on the solvatochromic behavior of the boronic acid esters was investigated. To separate the individual solvation effects we used the simplified Kamlet–Taft equation[25] (eq 1) from which the coefficients of the individual interaction contributions can be determined using multiple correlation analysis.[18,19]

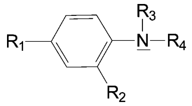
$$\tilde{\nu}_{\max} = \tilde{\nu}_{\max,0} + a\alpha + b\beta + s\pi^* \qquad (1)$$

$\tilde{\nu}_{\max}$ is the longest wavelength UV/vis absorption maximum of the compound measured in a particular solvent, $\tilde{\nu}_{\max,0}$ is that of a nonpolar reference solvent, α is the hydrogen-bonding acidity, β describes the hydrogen-bonding basicity, and π^* describes the dipolarity/polarizability of the solvent. a, b, and s are the solvent-independent correlation coefficients, which allow the effects of a particular parameter on the solvatochromic properties of the compounds to be determined.

According to the literature,[29,32] the class of compound to be investigated should be readily accessible by nucleophilic substitution of fluoronitroaromatics with 1-aminopropane-2,3-diols and 2-aminopropane-1,3-diol (serinol) (Scheme 1).

Carrying out the synthesis according to Scheme 1, however, was not so trivial as many experiments performed using literature procedures in solvents such as DMSO, NMP, or DMF failed to allow clean isolation of products, and consequently chiral compounds could not be obtained enantiomerically pure. Finally, the method of choice was found to involve performing the reaction in the melt with $CaCO_3$ as the catalyst. Enantiomerically pure and racemic nitroanilines with 1,2- and 1,3-diol functions were thus obtained in high purity (Table 1).

TABLE 1. Synthesized 1,2- and 1,3-Diol-functionalized Nitroanilines by Nucleophilic Aromatic Substitution in the Melt According to Scheme 1



	R_1	R_2	R_3	R_4
1	NO_2	H	CH_3	*rac*-$CH_2(CHOH)CH_2OH$
2	H	NO_2	CH_3	*rac*-$CH_2(CHOH)CH_2OH$
3	NO_2	NO_2	CH_3	*rac*-$CH_2(CHOH)CH_2OH$
4	NO_2	H	H	(*R*)-$CH_2(CHOH)CH_2OH$
5	H	NO_2	H	(*R*)-$CH_2(CHOH)CH_2OH$
6	NO_2	NO_2	H	(*R*)-$CH_2(CHOH)CH_2OH$
7	NO_2	H	H	(*S*)-$CH_2(CHOH)CH_2OH$
8	H	NO_2	H	(*S*)-$CH_2(CHOH)CH_2OH$
9	NO_2	H	H	$CH(CH_2OH)_2$
10	H	NO_2	H	$CH(CH_2OH)_2$
11	NO_2	NO_2	H	$CH(CH_2OH)_2$

Complete retention of the (*R*)-configuration during nucleophilic substitution was established unambiguously by X-ray structure analysis of (*R*)-*N*-[1-(2,3-dihydroxypropyl)]-2-nitroaniline (**5**) (Flack-x: 0.1(15)).

The crystal structure of **5** (Figure 1A) shows weak intermolecular hydrogen bonding interactions between O1–H1⋯O1A and O2–H5⋯O2A (O1⋯O1A 263.6(2), O2⋯O2A 267.2(2) pm). The molecules are arranged in a helical chain, whereby the aryl rings are on the exterior and are parallel to one another. Overall there is a double-helix structure (Figure 1B). Weak intramolecular hydrogen-bonding interactions between N1–H8⋯O3 (N1⋯O3 260.8 (2) pm) and intermolecular hydrogen-bonding

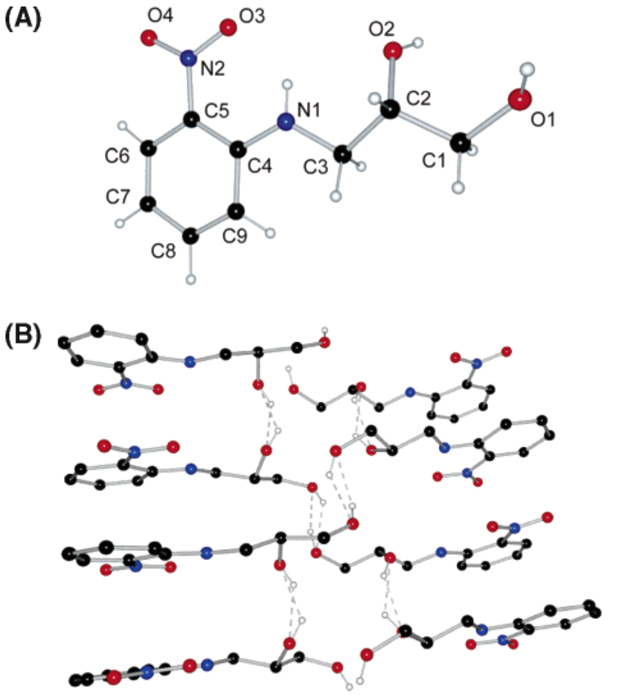


FIGURE 1. (A) X-ray crystal structure of (*R*)-*N*-[1-(2,3-dihydroxypropyl)]-2-nitroaniline (**5**), crystals from acetonic solution, and (B) helical structure of **5**.

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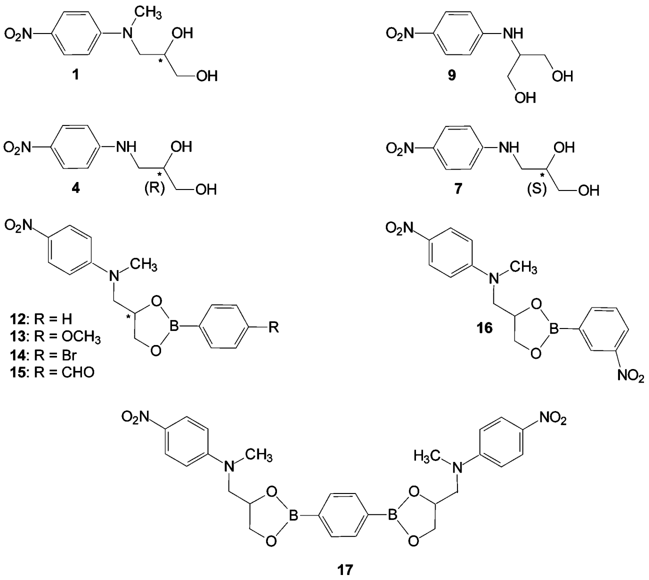
SCHEME 2. Studied Compounds Regarding Their Solvatochromic Behavior



interactions between the oxygen of the nitro group and the hydrogen atoms on C1A and C9A of the neighboring molecule (O4···C1A 321.7(2), O3···C9A 342.5(2) pm) lead to further binding of the helices in the periphery.

Comparable X-ray structure analyses of 1,2-diol-functionalized nitroanilines have not been described. A paper by Ojala et al. reports the crystal structure of a sugar-functionalized aniline whereby the 4-nitroaniline unit is bonded to C1 of the sugar forming a β-N glycoside.[33]

To demonstrate the concept of reversible combination, reactions of compound **1** with variously substituted phenylboronic acids were investigated. The esterification is an equilibrium reaction so the water formed was removed by azeotropic distillation from the reaction mixture.[34] Thermogravimetric analysis of the boronic esters obtained showed that the thermal stability was considerably higher than that of the starting diols. Decomposition of the esters begins at about 220 °C, whereas the 1,2-diol-functionalized nitroanilines began to decompose at ca. 150 °C.

Thus, treatment with arylboronic acids not only protects the 1,2-diol function but also increases the stability. In further work it will be shown how, building on the Lego principle, chiral information on chromophoric structures can be integrated into nanosystems.

For the solvatochromic investigations we chose the four new nitroaniline derivatives **1**, **4**, **7**, and **9** and the boronic esters **12**−**17** synthesized from **1** (Scheme 2), and the measurements were taken in 27 different solvents to determine the coefficients a, b, and s in eq 1.

Because of a high polarity and HBD/HPA capacity of the diol-functionalized chromophore, it is likely that association will occur in nonpolar solvents, and this can have an effect on the UV/vis absorption maximum. For this reason, very low concentrations ($c \sim 10^{-5}$ M) of the compounds were used for the UV/vis measurements. This posed particular requirements on the purity of the solvents. The UV/vis absorption maxima were then correlated with the Kamlet−Taft solvent parameters.[35]

The results of the multiple square correlation analyses are shown in Table 2.

TABLE 2. Values of the Solvent-Independent Correlation Coefficients (a, b, and s of the Kamlet−Taft Parameters α, β, and π^*), Solute Property of a Reference System $\tilde{\nu}_{\max,0}$, Standard Deviation (sd), Correlation Coeffiecent (r), and Number of Solvents (n) for the Solvatochromism of Compounds 1, 4, 7, 9, and 12−17 (Scheme 2)

compd	$\tilde{\nu}_{\max,0}$	a	b	s	n	r	sd
1	27.8	−0.61	−0.78	−2.70	26	0.96	0.24
4	28.9	−0.66	−1.62	−2.64	26	0.96	0.26
7	28.9	−0.71	−1.65	−2.57	25	0.96	0.26
9	29.0	−0.59	−1.65	−2.69	25	0.95	0.27
12	28.2	−0.62	−1.01	−2.94	25	0.98	0.21
13	28.0	−0.88	−0.83	−2.71	27	0.96	0.26
14	28.5	−0.44	−1.38	−3.19	24	0.97	0.22
15	28.3	−0.89	−1.09	−2.96	26	0.97	0.24
16	28.3	−0.79	−1.11	−3.02	27	0.96	0.30
17	28.3	-3.8×10^{-4}	−1.47	−2.99	24	0.96	0.24

The correlation coefficient r is greater than 0.95 for LSE relationships, which indicates a high validity of the multiparameter equations and allows significant conclusions to be drawn. The arrangement of the nonpolar solvents, such as benzene, toluene, tetrachloromethane, triethylamine, diethyl ether, or p-xylene, in the LSE relationship shows that no significant contribution by dimers or associated compounds to the solvatochromism could be observed. As expected, all compounds show positive solvatochromism with regard to the π^*-parameter, which correlates with the higher dipole moment of the electronically excited state, and it was expected that p-nitroaniline derivatives in particular could be used to set up the π^*-polarity scale.[24−26] Protic solvents, which can act as hydrogen bond donors (HBD) and electron-pair acceptors (EPA), also interact with the oxygen atoms of the nitro groups (a is negative). However, the effect of the a coefficient is only very small and, in comparison to s and b, is of little significance.

The highly positive solvatochromic effect of the β-parameter in the 1,2-diol-and N-methyl-substituted p-nitroaniline derivative **1**, caused by specific solvation of the diol groups by hydrogen bonding to the solvent, is new and noteworthy. We found a similar effect of the β-parameter in investigations of the solvatochromism of N-(2-hydroxyethyl)-substituted Michler's ketone derivatives.[36,37] The stronger contribution of the HBA capacity (β-term) on the solvatochromism for compounds **4**, **7**, and **9** was expected and can be readily explained through NH−solvent interactions.[38−41]

The solvatochromism of the boronic esters **12**−**17** also surprisingly shows a clear effect of the basicity of the

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solvent on the positive solvatochromic shift, although both OH groups are completely protected. The influence of the β-term (basicity) of the solvent on the contribution to the bathochromic shift of compounds **12**−**15** can be explained in two ways. First, the boron atom can build up a five-membered ring involving the amino nitrogen atom of the aromatic ring. Then the external base competes with the lone electron pair of the amino group. Some sugar indicators are based on this mechanism.[10,11] Since that intramolecular boron atom complex formation takes place, a significant hypsochromic UV/vis shift of the compounds **12**−**15** compared to compound **1** is expected. However the difference of $\Delta\tilde{\nu}$ measured in various solvents (Table 2) does not exceed 400 cm^{-1}. In dichloromethane or toluene the effect on the shift of the UV/vis band is negligible.

Second, it is possible that the specific solvation of the sp^2-hybridized boron by electron pairs of bases increases the electron-donating properties of the neighboring amino group. This effect is particularly clear in the case of the 1,4-phenyldiboronic-acid-bridged bis(4-nitroaniline) derivative. Apparently, the electron-donating effect of the complexed boronic acid groups is increased by a second boronic acid group, which has also been discussed briefly by Hoeg-Jensen for diboronates.[42] In the case of the *p*-methoxy group (compound **13**), complex formation at the boron atom is obviously compensated for by the +M effect (lower *b* value). In other cases, the effect of the substituent on the phenylboronic acid on the *b* coefficient is within experimental error. To support the hypothesis of complex formation at boron, 1 equiv of strongly basic fluoride in each case was added to compounds **12**−**17**.

Fluoride should show this effect particularly clearly, as many boron-based fluoride sensors are based on this complex formation.[43,44] The effect of fluoride ion on the solvatochromic behavior of compounds **12**−**17** was determined using tetra-*n*-butylammonium fluoride (n-$Bu_4N^+F^-$) in thf. The pure boronic ester **13** has an absorption maximum at $\lambda_{max} = 385$ nm in thf. On addition of n-$Bu_4N^+F^-$, the whole UV/vis band clearly undergoes a bathochromic shift to $\lambda_{max} = 400$ nm ($\Delta\tilde{\nu} = 970$ cm^{-1}) (Figure 2). For the other compounds, the following $\Delta\nu$ values were found: **12** (970 cm^{-1}), **14** (1230 cm^{-1}), **15** (960 cm^{-1}), **16** (580 cm^{-1}), and **17** (1160 cm^{-1}). The compounds **14** and **17** have the highest *b* coefficients; consequently, they also show the strongest UV/vis shift on addition of fluoride. An excess of fluoride does not lead to any further shift of the UV/vis band. The pure 1,2-diol derivative **1** shows a weaker bathochromic shift on addition of fluoride ($\Delta\tilde{\nu} = 323$ cm^{-1}). We explain this effect by the fact that fluoride ions interact with the hydroxy groups similar to HBA solvents.

These results support the interpretation that complexation of the boron atoms with bases strengthens the electron-donating effect of the amino group and thus the push−pull character of the aromatic system. When ordered structures, such as polar crystals, are assembled using these building blocks, this effect can be significant.

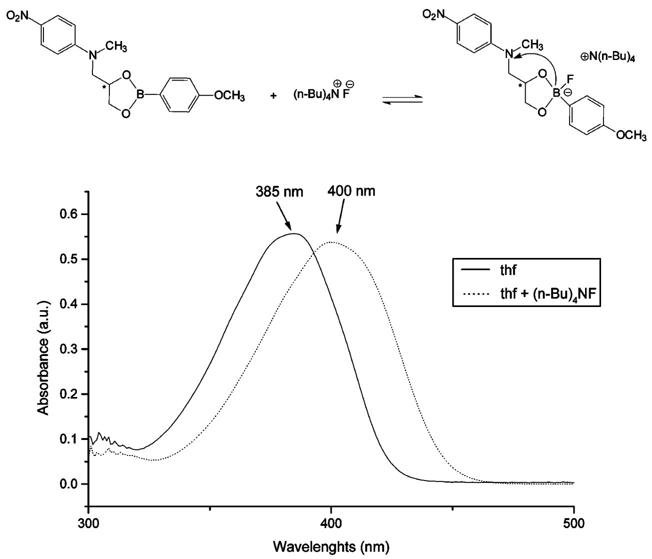

FIGURE 2. (A) UV/vis absorption spectra of compound **13** in tetrahydrofuran (THF) and after addition of the strong coordinative base fluoride (tetra-*n*-butylammonium fluoride).

In the case of compound **17** which contains no N−H groups, the measurable effect of the basicity of the solvent will have on $\tilde{\nu}_{max}$ is of the same order of magnitude as in the use of NH-acidic substituents.

The results of this work show that the functionalization of the amino nitrogen of *p*-nitroaniline derivatives with polar groups which are not in direct n−π conjugation with the aromatic system also affects the solvatochromism of the pull−push system in a complex fashion.

Experimental Section

General Procedure for Synthesis of Diol-Functionalized Nitroanilines. All diolfunctionalized nitroanilines were synthesized by the same experimental procedure.

The aminopropandiol (5.5×10^{-3} mol) and the corresponding fluoronitrobenzene were heated to 130 °C with calcium carbonate in the melt for 8 h. After being cooled to room temperature, the mixture was washed at first with water and then with diethyl ether. After that, 40 mL of acetone was added, whereas the nitroaniline derivatives were solved and it was possible to remove the calcium fluoride from the mixture by filtration. The solvent was evaporated, and the corresponding 1,2- and 1,3-diolfunctionalized nitroanilines were obtained as solids and oils, respectively.

General Procedure for Synthesis of the Boronate Esters. Equimolar amounts of compound **1** and the corresponding aromatic boronic acid were suspended in 80 mL of toluene and heated to 100 °C. The mixture were stirred for 1 h at this temperature, whereby a clear solution were formed. The water formed was removed by azeotrop distillation from the reaction mixture. After the mixture was cooled to room temperature, the yellow precipitate formed was filtered, washed with toluene, and dried in air to afford the corresponding ester of the boronic acid.

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Supporting Information Available: General experimental procedures, characterization data of compounds **1**−**17** thermogravimetric analysis of **1** and **12**−**17**, all UV/vis data, Uv/vis spectra of **1** on addition of fluoride and X-ray crystallographic data of **5** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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