Chiral, Solvatochromic Schiff Bases Containing the (S)-Proline or (R)-3-Aminopropane-1,2-diol Functionality

Stefan Spange,* Katja Schreiter, Katja Hofmann

Department of Polymer Chemistry, Institute of Chemistry, Chemnitz University of Technology, 09111 Chemnitz, Germany
Fax +49(371)5311642; E-mail: stefan.spange@chemie.tu-chemnitz.de

Received 26 April 2006
Dedicated on the occasion of the 65th birthday of Prof. D. Hoppe, Münster, Germany

Abstract: Chiral 4-nitroaniline derivatives 2a,b containing amino acid and 1,2-diol functionalities have been synthesized by specific nucleophilic substitution of 1-fluoro-4-nitrobenzene (1) with (S)-proline or (R)-3-aminopropane-1,2-diol. Following reduction of the nitro groups under very mild conditions, the corresponding ω-phénylendiamine derivatives 3a,b were obtained which are very sensitive to oxidation. Thus, 3a,b were converted in situ into chiral, solvatochromic Schiff bases.

Key words: amino acids, amino alcohols, chirality, nucleophilic aromatic substitution, Schiff bases

The development of ultraviolet/visible (UV/vis) sensor probes for biologically active compounds, such as amino acids, sugars, and related structures, is an important topic that has been studied intensively in recent years.1–3 There are two types of UV/vis probe: Fluorophores, which can interact with sequence specific sites of DNA or protein and either show a significant new UV/vis signal or the fluorescence is specifically quenched.4–10 Alternatively, dipolar solvatochromic UV/vis absorption probes are suitable for the observation of graduate changes of polarity in their environment. One challenge is the introduction of chiral moieties into the dye in such a way that they are part of the chromophoric system in order to show the potential for genuine chiro-solvatochromism in molecular recognition.11–14 As yet there is no broad availability of genuine, chiral solvatochromic probes, which can be tailored by consecutive functionalization reactions.

Herein we show that N-substituted 4-nitroanilines 2a,b (Scheme 1) can be used as chiral building blocks and condensed with 4-nitrocinnamaldehyde to construct enantiomerically pure solvatochromic Schiff bases (Scheme 2).

For our initial studies, we chose an amino acid and a chiral 1,2-diol functionality as chiral building blocks, because they can readily undergo consecutive tailoring. N-Linked amino acids can be coupled with other amino acids, dipeptides, or oligopeptides via the remaining C-terminus, which allows the extension of the recognition sequences.6 1,2-Diol functionalities can be reversibly coupled with aldehydes, boronic acids, and structurally related compounds.15,16

SYNTHESIS 2006, No. 13, pp 2100–2102
Advanced online publication: 08.06.2006
DOI: 10.1055/s-2006-942408; Art ID: C01706SS
© Georg Thieme Verlag Stuttgart · New York
have a negative influence on both the consecutive Schiff base condensation reaction with 4-nitrocinamaldehyde and the UV/vis spectra of the target products. Thus, 3a,b were coupled directly with 4-nitrocinamaldehyde after the reduction process without isolation to give Schiff bases 4a,b, and this is possible because the conversion of 2a and 2b into 3a and 3b is quantitative.

The structures of the target compounds 4 were confirmed by high-resolution 1H and 13C NMR spectroscopy. X-ray structure analysis confirms the retention of the chiral center.

The target compound containing the (S)-proline unit, 4a, was obtained as the ammonium salt, which was used for the UV/vis spectroscopic study to investigate the impact of the negative charge of the carboxylate group on the solvatochromism of the target compounds. A detailed investigation and interpretation of the manifold influence of the environment on the solvatochromism of 4a,b and related compounds by means of the Kamlet–Taft LSE (linear solvation energy) relationship will be reported.\textsuperscript{11,16,21,22}

All commercial reagents and solvents were used without further purification, they were purchased from the following suppliers: Fluka: (R)-3-aminopropane-1,2-diol, Lancaster: 4-nitrocinamaldehyde, ABCR: 1-fluoro-4-nitrobenzene, Acros: (–)-(S)-proline. Methanol was dried with sodium and distilled under argon. All melting points were uncorrected. 1H NMR and 13C NMR spectra were measured in DMSO-d$_6$; IR spectra were recorded on a FTIR instrument using KBr pellets. Elemental analysis was determined with a Vario-EL analyzer.

\textbf{Scheme 2}  Reduction of the nitroaniline derivatives 2a,b and formation of the Schiff bases 4a,b

The color of 4a changes from yellow ($\lambda_{max} = 428$ nm (CH$_2$Cl$_2$)) to blue ($\lambda_{max} = 573$ nm (1,1,1,3,3,3-hexafluoropropan-2-ol)) and of 4b from yellow ($\lambda_{max} = 433$ nm (CH$_2$Cl$_2$)) to violet ($\lambda_{max} = 525$ nm (1,1,1,3,3,3-hexafluoropropan-2-ol)). Obviously, the impact of the solvation upon the carboxylate group by the strong hydrogen bond donor (HBD) solvent 1,1,1,3,3,3-hexafluoropropan-2-ol is clearly measurable, because the bathochromic shift of 4a ($\Delta\lambda_{max} = 145$ nm) is evidently larger than for 4b ($\Delta\lambda_{max} = 92$ nm). A detailed investigation and interpretation of the manifold influence of the environment on the solvatochromism of 4a,b and related compounds by means of the Kamlet–Taft LSE (linear solvation energy) relationship will be reported.\textsuperscript{11,16,21,22}

All commercial reagents and solvents were used without further purification, they were purchased from the following suppliers: Fluka: (R)-3-aminopropane-1,2-diol, Lancaster: 4-nitrocinamaldehyde, ABCR: 1-fluoro-4-nitrobenzene, Acros: (–)-(S)-proline. Methanol was dried with sodium and distilled under argon. All melting points were uncorrected. 1H NMR and 13C NMR spectra were measured in DMSO-d$_6$; IR spectra were recorded on a FTIR instrument using KBr pellets. Elemental analysis was determined with a Vario-EL analyzer.

\textbf{Scheme 2}  Reduction of the nitroaniline derivatives 2a,b and formation of the Schiff bases 4a,b

The color of 4a changes from yellow ($\lambda_{max} = 428$ nm (CH$_2$Cl$_2$)) to blue ($\lambda_{max} = 573$ nm (1,1,1,3,3,3-hexafluoropropan-2-ol)) and of 4b from yellow ($\lambda_{max} = 433$ nm (CH$_2$Cl$_2$)) to violet ($\lambda_{max} = 525$ nm (1,1,1,3,3,3-hexafluoropropan-2-ol)). Obviously, the impact of the solvation upon the carboxylate group by the strong hydrogen bond donor (HBD) solvent 1,1,1,3,3,3-hexafluoropropan-2-ol is clearly measurable, because the bathochromic shift of 4a ($\Delta\lambda_{max} = 145$ nm) is evidently larger than for 4b ($\Delta\lambda_{max} = 92$ nm). A detailed investigation and interpretation of the manifold influence of the environment on the solvatochromism of 4a,b and related compounds by means of the Kamlet–Taft LSE (linear solvation energy) relationship will be reported.\textsuperscript{11,16,21,22}

All commercial reagents and solvents were used without further purification, they were purchased from the following suppliers: Fluka: (R)-3-aminopropane-1,2-diol, Lancaster: 4-nitrocinamaldehyde, ABCR: 1-fluoro-4-nitrobenzene, Acros: (–)-(S)-proline. Methanol was dried with sodium and distilled under argon. All melting points were uncorrected. 1H NMR and 13C NMR spectra were measured in DMSO-d$_6$; IR spectra were recorded on a FTIR instrument using KBr pellets. Elemental analysis was determined with a Vario-EL analyzer.

\textbf{Scheme 2}  Reduction of the nitroaniline derivatives 2a,b and formation of the Schiff bases 4a,b
vent was evaporated from the filtrate to give 2b as a yellow solid; yield: 0.74 g (63%); mp 138–141 °C.

IR (KBr): 3424, 3314, 3105, 2926, 1603, 1548, 1467, 1335 cm⁻¹.


Acknowledgment

Financial support by the Deutsche Forschungsgemeinschaft, Bonn and the Fonds der Chemischen Industrie, Frankfurt am Main, is gratefully acknowledged.

References