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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2149–2153

Synthesis and fluorescence properties of naphthalimide-containing Tröger's bases

Nicholas R. Deprez,[a] Kristy A. McNitt,[a] Matthew E. Petersen,[a] Robert G. Brown[b,*] and David E. Lewis[a,*]

[a]*Department of Chemistry, University of Wisconsin-Eau Claire, Eau Claire, WI 54702-4004, USA*
[b]*School of Applied Sciences, University of Glamorgan, Pontypridd, Wales, UK CF37 1DL*

Received 23 November 2004; revised 12 January 2005; accepted 12 January 2005

Abstract—Tröger's bases based on the naphthalimide fluorophore have been prepared from *N*-alkyl-4-amino-1,8-naphthalimides. The fluorescence emission intensity of these dyes is highly medium dependent. In cyclohexane, these dyes emit near 440 nm with high quantum yields; addition of cosolvents reduces the fluorescence intensity near 440 nm and leads to increased fluorescence intensity around 480 nm.
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Tröger's bases, first synthesized by Tröger in 1887,[1] have historically been of interest due to the presence of the configurationally stable chiral nitrogens in the dibenzodiazocine nucleus, and have been described as 'fascinating molecules'.[2] Over the past several years, the ease of synthesis of the symmetrical Tröger's bases and the rigidity of the chiral dibenzodiazocine nucleus have made these compounds attractive systems for exploitation in a variety of guest–host molecules, forming the scaffold for the formation of a variety of compounds, including synthetic receptors.[3]

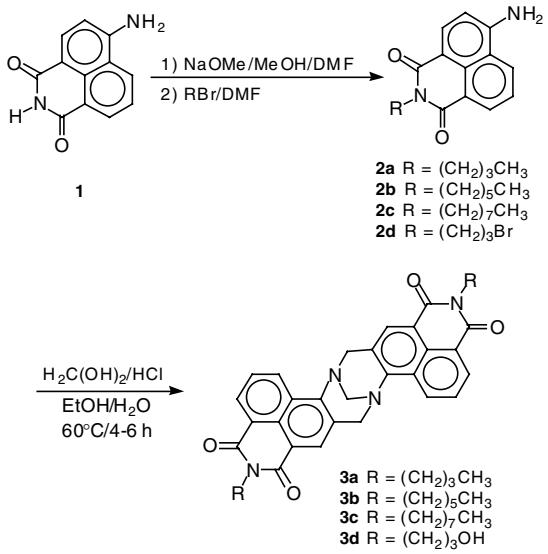
Prior to the report of Webb and Wilcox[4] in 1990 describing a general method for the synthesis of unsymmetrically substituted dibenzodiazocines, the synthesis of Tröger's bases had necessarily led to the formation of C_2-symmetric compounds. The ability to prepare non-C_2-symmetric Tröger's bases has led to a rich chemistry of these compounds as 'nanoscale structural units'.[5] During the same time period, the synthesis of Tröger's bases from a variety of aminoheterocycles has been carried out; some of these compounds have been shown to bind to DNA.[6] Abella et al. have very recently reported the preparation of three Tröger's bases, which undergo excited state intramolecular proton transfer[7,8] where it is interesting to note that the fluorescence properties of one of the systems (based on 2-(2′-hydroxyphenyl) benzothiazole) is considerably modified by its incorporation into the Tröger's base. The recent work of Wärnmark has provided new methods for the synthesis of halogenated Tröger's bases, and, by selective lithium-halogen exchange, of unsymmetrically substituted Tröger's bases, which has expanded the structural features accessible in these compounds to include acid-sensitive functionality.[10]

We have been interested for a number of years in the synthesis and properties of naphthalimides, particularly with amino-substituents in the 4-position. These compounds find widespread utility, for example, as antiviral agents,[9] fluorescent sensors for metal ions[11] and pH[12] and as elements in the design of molecular logic gates.[13] The emission properties of these systems are strongly influenced by the solvent and by the nature and degree of substitution on the nitrogen[14] since the ability of the compounds to form twisted charge transfer states may be a major determinant of the excited state properties.

With this in mind, the stereochemistry enforced on compounds which incorporate the Tröger's base structure suggested itself as being of interest in the design of novel amino-substituted naphthalimides. We report here the synthesis and some photophysical measurements on compounds of this type.

* Corresponding authors. Tel.: +1 715 836 4744; fax: +1 715 836 4979 (D.E.L.); tel.: +44 (0)1443 482 280; fax: +44 (0)1443 483 554 (R.G.B.); e-mail addresses: rgbrown@glam.ac.uk; lewisd@uwec.edu

0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.01.166

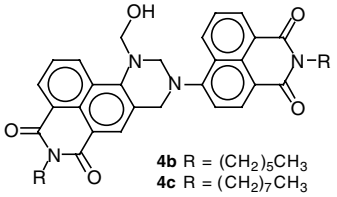


Scheme 1. Synthesis of fluorescent Tröger's bases.

The C_2-symmetric Tröger's bases of this study were prepared from 4-amino-1,8-naphthalimide by standard methods (Scheme 1).

Alkylation of 4-amino-1,8-naphthalimide under Gabriel conditions[9,15,16] was followed by dimerization of the *N*-alkyl-4-amino-1,8-naphthalimides into the Tröger's bases by heating with formaldehyde and hydrochloric acid in ethanol solution. The formation of the Tröger's base was confirmed by the ^{1}H NMR spectrum: the protons of the diazocine ring system appear as a singlet and a well-separated AB quartet (Fig. 1).

When the reaction is carried out by stirring the mixture for 15 h without external heating, naphthalimide **2a** is converted completely to the Tröger's base, but naphthalimides **2b** and **2c** are converted into very slightly soluble *seco*-Tröger's bases, **4b** and **4c**, presumably due to their precipitation from the reaction mixture as they are formed at this lower temperature. Similar compounds were obtained by Miller and Wagner[17] during their attempted preparation of halogenated Tröger's bases from haloanilines. Like these workers, we have been unable to convert these compounds further into the Tröger's bases, and agree with their conclusion that their status as intermediates in the formation of the dibenzodiazocines is problematic. Unexpectedly, the ω-bromoalkyl group of naphthalimide **2d** underwent nucleophilic substitution during the formation of the Tröger's base, giving the difficultly soluble diol **3d** as the major product; we were unable to obtain this compound pure by ^{1}H NMR, although the same sample gave satisfactory microanalysis.



Unlike their fluorescence spectra, the electronic *absorption* spectra of the Tröger's bases are relatively insensitive to solvent. For example, except for cyclohexane (λ_{max} 374 nm), the absorption maximum of **3a** does not change appreciably (λ_{max} 384 ± 3 nm) in a range of solvents from toluene to ethanol and dimethylformamide, and the ε_{max} for compound **3a** is $1.6 \pm 0.2 \times 10^4$ over the same range of solvents (Table 1). The recorded extinction coefficients are of a magnitude which is entirely consistent with other naphthalimide-based systems[11,13b,14] but the somewhat blue-shifted absorption maxima and the relative insensitivity of this parameter

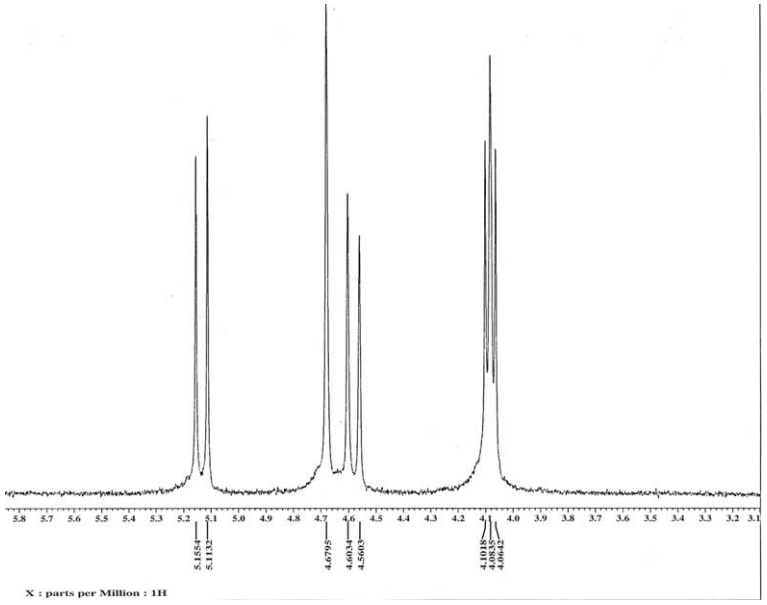


Figure 1. Diazocine proton resonances of **3b**.

Table 1. Absorption maxima [λ_{abs}], molar absorptivities [ε_{max}], emission maxima (λ_{em}) and fluorescence quantum yields [Φ] for compound **3a** in selected solvents

Solvent	λ_{abs}	ε_{max}	λ_{em}	Φ
Cyclohexane	374	1.64×10^4	442	0.938
Toluene	382	1.49×10^4	457	0.431
Dichloromethane	384	1.69×10^4	492	0.194
Ethyl acetate	381	1.66×10^4	500	0.129
Acetonitrile	384	1.68×10^4	524	0.0185
Ethanol	383	1.75×10^4	528	0.0046
Dimethylformamide	387	1.40×10^4	530	0.0107

to the solvent suggests that the stereochemistry imposed by the Tröger's base is having a noticeable effect.

The fluorescence spectra of these compounds are rather insensitive to the effects of small changes in the structure of the side chains of the Tröger's base itself, and compounds **3a**–**d** all have similar fluorescence spectra. However, this is not the case with the effects of solvent: in contrast to the absorption spectra, the fluorescence spectra of these compounds are *highly* solvent dependent, as the data in Table 1 show.

Thus, the wavelength of maximum emission of **3a** changes by almost 100 nm as the solvent is changed, and the fluorescence quantum yield changes by two orders of magnitude depending on solvent. However, the fluorescence quantum yield does not correlate well with the known ability of the solvent to quench fluorescence. For example, the relative fluorescence quantum yield of the Tröger's base **3a** is 0.938 in toluene and yet it is only 0.0046 in ethanol, a solvent not noted for fluorescence quenching. The behavior of **3b**–**d** in cyclohexane and other solvents is very similar to that of **3a**. These quantum yield changes are entirely consistent with the photophysical data reported by Saha and Samanta for a range of 4-amino-naphthalimides[14b] (and with unpublished data of our own). A decrease in fluorescence quantum yield of two orders of magnitude as one moves from non-polar, non-interacting solvents such as hexane or cyclohexane to polar and/or protic solvents such as ethanol and acetonitrile is expected. This decrease is almost entirely due to an increase in non-radiative deactivation of the naphthalimide excited singlet state.[14b] Saha and Samanta discuss the possible reasons for the increased non-radiative rate constant in polar solvents and conclude that this is due to an increased rate for nitrogen inversion rather than twisting of the 4-amino group with respect to the naphthalimide ring. Both of these processes will be disfavored in the Tröger's bases reported here, yet there is the strong similarity between the fluorescence quantum yields of our Tröger's bases and the naphthalimides of Saha and Samanta. We do not yet have the fluorescence lifetime data to complement the quantum yields and thus enable us to calculate non-radiative rate constants, but our expectation is that the emission properties of our Tröger's bases will also be controlled by their non-radiative decay rates. If this proves to be the case, then a different mechanism (e.g., intramolecular excimer formation) may be required to explain the observed data.

This type of behavior (red-shifting the wavelength of maximum emission intensity and lowering of the maximum intensity of emission) is exhibited by these dyes whenever another organic compound is added to the cyclohexane solution. Except for nitrobenzene and aniline, which quench the fluorescence of **3b** completely, a wide variety of liquids from alkene hydrocarbons and alkyl halides to arenes (toluene, 1-methylnaphthalene), carbonyl compounds (cyclohexanone, acetophenone, ethyl acetate, *o*-chlorobenzaldehyde), nitriles (acetonitrile, 2-*endo*-5-norbornene-2-carbonitrile, benzonitrile, *o*-tolunitrile), and alcohols (1-butanol, cyclohexanol, 2-methyl-2-pentanol, 2-methyl-3-pentanol, 3-methyl-3-pentanol, 4-methyl-2-pentanol) have shown qualitatively the same effects on the fluorescence of **3b** as those summarized in Table 1 have on the fluorescence of **3a**. Moreover, often only small quantities of the added compound (typically, millimolar concentrations—much less than is required to affect the dielectric constant of the solution markedly) cause a significant change in the fluorescence spectra, which suggests that this is not necessarily a bulk dielectric effect, but a complexation of some sort.

The observations of **3b** in cyclohexane with added toluene (Fig. 2) are typical. While the fluorescence emission intensity at 429 nm decreases on addition of these compounds, the increase in fluorescence intensity around 480 nm suggests that the mechanism for these changes is not simple quenching, but the formation of a new fluorescent species. The emission curves at low concentration appear to pass through an 'isosbestic point' near 458 nm, which may be consistent with there being a simple equilibrium between two fluorescent species. We are investigating the import of this observation.

While we have not established this unequivocally, the fluorescence emission intensity at constant wavelength appears to reflect the fluorescence quantum yield in these compounds. In such a case, the Stern–Vollmer relationship predicts that a plot of $[I(0)/I(c)]-1$ versus toluene concentration, where $I(0)$ is the emission intensity in the absence of toluene, and $I(c)$ is the emission intensity in the presence of c M toluene, should be a straight line passing through the origin if this is simple collisional quenching. In the case of added toluene, the

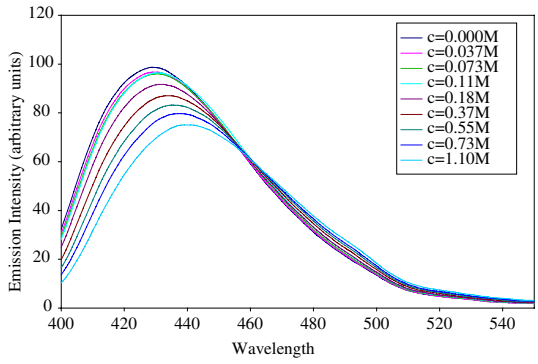


Figure 2. Fluorescence emission spectra of **3b** in cyclohexane in the presence of toluene.

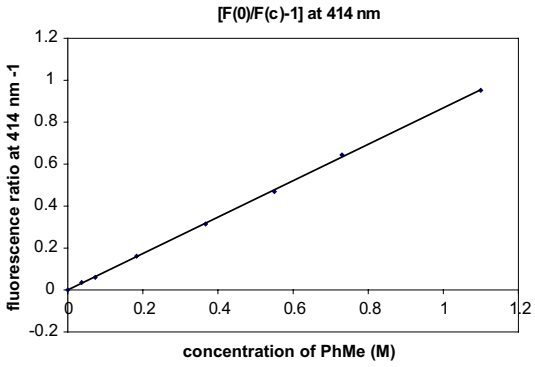


Figure 3. Ratio of fluorescence emission at 414 nm in presence of varying amounts of toluene versus toluene concentration.

plot of this function at several different wavelengths is, indeed, linear (Fig. 3 shows the plot at 414 nm, the wavelength where the difference in fluorescent intensity as revealed by difference plots is at a maximum), consistent with simple collisional quenching. This is also consistent with the formation of a simple 1:1 complex of the Tröger's base and toluene.

Similar plots for the data obtained with 1-butanol (chosen over ethanol since it is miscible with cyclohexane) are curved, and there is no single 'isosbestic point' in the fluorescence emission spectra, although there is a suggestion that there is one 'isosbestic point' at concentrations below 1.1 mM, and another which occurs above 3.7 mM. This suggests that the interaction with 1-butanol is almost certainly not as simple as that with toluene, and that more than one species is formed in this case. Certainly, the interaction of butanol with the Tröger's base cannot be simple collisional quenching of fluorescence.

While the fluorescence emission of these dyes responds to a wide variety of added compounds, what is not apparent is any definitive structural feature in the added compounds that leads to the change in fluorescence behavior. The results obtained using **3b** with dicyclopentadiene and 1-bromooctane suggest that non-conjugated π bonds and simple alkyl halides have minimal effects. The addition of arenes, alcohols, ketones, or nitriles all leads to a reduction in the fluorescence emission intensity, and to a red shift in the wavelength of maximum fluorescence emission, with the most electrophilic species giving rise to the most marked effects. Preliminary results with the series of isomeric methylpentanols suggest that there may be a modest steric effect operating. While it is tempting to suggest that there is an electrophile–nucleophile interaction between the added compound and one of the nitrogens of the Tröger's base, the data to date are marginal in support of such a model. The origins of these effects are under investigation.

We thank the National Institutes of Health (Grant # 1 R15 DA013578-01) and the University of Wisconsin—Eau Claire Office of Research and Sponsored Programs for financial support of this research.

Supplementary data

(1) Detailed experimental procedures for preparing **3a**–**d**, **4b**,**c**. (2) ^{1}H NMR spectra of **3a**–**d**, **4b**,**c**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.166.

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