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Photophysical behavior of a potential drug candidate, *trans*-[2-(4-methoxystyryl)]quinoline-1-oxide tuned by environment effects

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ABSTRACT

Styryl and/or quinoline structural fragments, present in a large number of bioactive substances, inspired the design of various new drug candidates. In this paper, we describe the photophysical behavior of *trans*-[2-(4-methoxystyryl)]quinoline-1-oxide (*trans*-MSQNO) on the basis of X-ray analysis data, theoretical calculations as well as steady state and time-resolved spectroscopy experiments in various media. The molecule crystallizes in orthorhombic unit cell containing eight molecules of *N*-oxide, space group *Pbca*. The N—O bond is substantially shorter in comparison with the N—O bond in the ZnTPP unit [1.3052(11) Å vs. 1.335(2) Å]. Variation of emission colors from the violet (~450 nm) through blue (480 nm), green (525 nm) and yellow (575 nm) is observed in different environments. Comparable values of lifetimes estimated both at ambient temperature and at 77 K suggest that excited state dynamics in this case is viscosity independent. DFT and TD DFT B3LYP/6-31G(d, p) calculations performed for four different *trans*-MSQNO rotamers in the gas phase, as well as nonpolar and polar media (PCM model) suggest that an equilibrium between them can be significantly altered even by a relatively weak interactions with the environment. It is suggested that varying intensity ratios of experimental absorption bands in different media may be due to the dominant share of one or more rotamers of the excited *trans*-MSQNO molecule. Gas phase calculations show also that the vertical $\pi\pi^*$, $S_0 \rightarrow S_1$, transition resulting from the HOMO → LUMO electronic configuration exhibits only a partial CT nature. On the other hand, in polar media, a substantial increment of excited state dipole moment of all rotamers compared to the ground state, its increase with increasing solvent polarity and a significant red shift in the absorption and emission spectra, point to the enhanced CT nature of the S_1 excited state. Hence, the *trans*-MSQNO molecule may be considered a subsequent styrylquinoline drug candidate where the CT drug-receptor interactions are of a high importance.

1. Introduction

Unique photophysical properties of functionalized styryl dyes with a differently substituted ($—C_6H_5—CH{=}C—$) fragment are a subject of several ongoing studies [1]. These potentially bioactive heterocycles may find application in various aspects of medicine and pharmacology [2,3]. Furthermore, substituted styryl dyes are also widely used in modern technologies such as production of laser discs [4,5], chemical sensors [6,7], OLEDs (Organic Light-Emitting Diodes) [8,9] or organic lasers [10]. A good example of the compound that may be explored in more than one of the abovementioned applications is *trans*-4-[*p*-[*N*-ethyl-*N*-(hydroxyethyl)aminostyryl]-*N*-methylpyridinium tetraphenylborate salt, which demonstrates not only the excellent lasing properties but also may be used in biomedical engineering as a fluorescent probe due to its fluorescence in the orange-red region (620–690 nm) [11–13].

Styryl derivatives, which show high visible fluorescence intensity in the green part of electromagnetic field, may find application in such biochemistry subfields as immunofluorescence and immunohistochemistry (for example 2-[4-(dimethylamino)styryl]-1-methylpyridinium iodide (DASPMI) or 2-[4-(dimethylamino)styryl]-1-methylquinolinium iodide (DASQMI) [14–16].

At this point we should also mention, the *trans*-[4-(dimethylamino)-4′-cyanostilbene] (DCS) system, one of the most thoroughly investigated stilbens that exhibits strong solvatochromism (large Stokes shift), relatively high quantum yield and a very short lifetime. These features suggest its use as a probe for the solvation processes and potential

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application in time-resolved spectroscopy, particularly as the probe in solvation dynamics and in the Kerr-gated emission spectroscopy [17–19].

Recently, we examined *trans*-4-[4′-(*N*,*N*-dimethylaminostyryl)] pyridine *N*-oxide (DPO) that also belongs to the class of stilbens. This molecule exhibits a strong dependence of stationary fluorescence from polarity of the solvent and demonstrates an effective charge transfer process between the dimethylamino group, as electron donor, and the N–O group of pyridine *N*-oxide moiety, as electron acceptor [20]. The DFT and TD DFT calculations have shown that in protic environment, the *trans*-DPO system forms the (1:1) hydrogen bonded complexes and undergoes the hydrogen bonded assisted charge transfer to a higher extent than in the free *trans*-DPO system.

Heterocyclic *N*-oxides, including styryl derivatives, often exhibit CT interactions that can be important for understanding the drug-receptor mechanism [21–24]. Recently, we also investigated CT behavior of the hybrid *trans*-MSQNO-ZnTPP complex, i.e. of *trans*-2-(4-methoxystyryl)quinoline-1-oxide (*trans*-MSQNO) and the ZnTPP unit.

In the hybrid, however, only weak CT interactions were observed. Hence, in search for possible stronger interactions of this type, we decided to investigate the excited state behavior of a free ligand, the unbounded *trans*-MSQNO molecule.

In this study, we report the X-ray structure of trans-2-(4-methoxystyryl)quinoline N-oxide along with the experimental results of steady state and time-resolved spectroscopy measurements in different media, further complemented by the results of the DFT and TD DFT B3LYP/6-31G(d,p) calculations.

2. Material and Methods

2.1. Synthesis

Synthesis of *trans*-2-(4-methoxystyryl)quinoline-1-oxide was performed on the basis of the method, described elsewhere [21]: 1.6 g (0.01 mol) of 2-methylquinoline-1-oxide and 1.9 g (1.7 mL, 0.014 mol) of 4-methoxybenzaldehyde were placed into 5 mL of 10% CH_3OK in methanol. The mixture was refluxed 3 h under nitrogen and then the solvent was evaporated in vacuum. The product was recrystallized from ethanol two times. Methanol and ethanol for synthesis and recrystallizations were of analytical grade (POCH, Sigma Aldrich).Yield: 1.94 g (70%), Yellow powder (m.p. 142.5–143 °C. Anal. calc. for $C_{18}H_{15}O_2N$ (%): C 77.96; O 11.54; N 5.05; H 5.45. Found (%): C 77.45; O 11.45; N 5.04; H 6.11.

2.2. X-ray Experiment

The crystal used for the measurements was cut from a larger crystal and had approximate dimensions 0.30 × 0.12 × 0.06 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα radiation source ($\lambda = 1.5418$ Å) with collimating mirror monochromators. A total of 2635 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 5 s per frame with a detector offset of ±40.8° and 20 s per frame with a detector offset of ±108.3°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1S. Data collection, unit cell refinement and data reduction were performed using Agilent Technologies CrysAlisPro V 1.171.37.31 [25]. The structure was solved by direct methods using SuperFlip [26] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2013 [27]. Structure analysis was aided by use of the programs PLATON98 [28] and WinGX [29]. The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2 × Ueq of the attached atom (1.5 × Ueq for methyl hydrogen atoms).

The function, $\Sigma w\,(|Fo|^2 - |Fc|^2)^2$, was minimized, where $w = 1 / [(\delta(Fo))^2 + (0.0535 * P)^2 + (0.9764 * P)]$ and $P = (|F_o|^2 + 2|F_c|^2) / 3$. $R_w(F^2)$ refined to 0.0964, with R(F) equal to 0.0349 and a goodness of fit, S = 1.03. The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992) [30]. All figures were generated using SHELXTL/PC [31].

2.3. Electronic UV–VIS Absorption Spectra

Electronic absorption spectra in solution were recorded on a CARY-50 UV–VIS (Varian) spectrometer at the concentration of 10^{-5} M of MSQNO. Solvents were of spectroscopic grade and used fresh as purchased (Merck, Uvasol)].

2.4. Steady State Emission Spectroscopy

Emission spectra both in solution and in the solid state were recorded on FSL920 combined fluorescence lifetime and steady state spectrofluorimeter (Edinburgh Instruments Ltd) using as excitation source Xe900, 450 W steady state xenon lamp (ozone free) with computer controlled excitation shutter and with spectral bandwidth of ≤5 nm for both excitation and emission spectra. The spectrofluorimeter was equipped with a temperature controlled the EHC-716 cell holder. Emission at 77 K was performed in a small EPR Dewar inserted into the controller of FSL920 set up (Edinburgh Instruments Ltd) while for the solid sample the front face geometry type holder was employed. Luminescence was detected using a red sensitive (185–850 nm) single photon counting photomultiplier tube (R928-Hamamatsu) in a Peltier cooled housing. Spectra were corrected for detector response and excitation source. Solvents were of spectroscopic grade and used fresh as purchased (Merck, Uvasol). The concentration of the studied solutions was about 10^{-5} M.

2.5. Time-resolved Spectroscopy

Fluorescence decay curves were recorded using nanosecond Time-Correlated Single Photon Counting (TCSPC) option of FSL920 setup

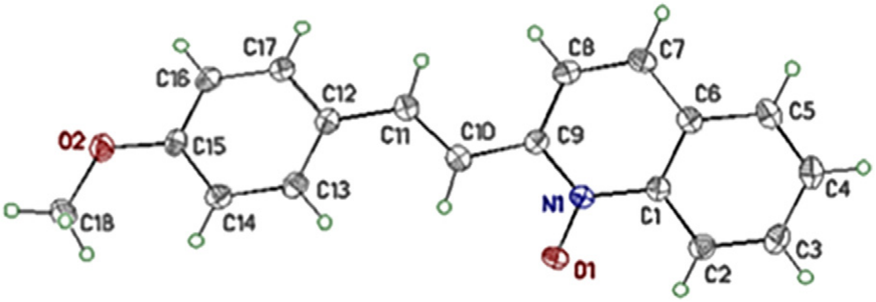

Fig. 1. ORTEP-view of *trans*-MSQNO showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.