Rational Design of Substituted *N*-Alkoxypyridine-2(1*H*)thiones with Increased Stability against Daylight†

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N-Alkoxypyridine-2(1*H*)thiones serve as valuable photochemical alkoxyl radical precursors in photobiological studies, but due to a broad absorption band at about 360 nm ($\pi \rightarrow \pi^*$ excitation), these molecules decompose readily when exposed to daylight. The goal of the present work is to propose *N*-alkoxypyridine-2(1*H*)thiones which due to a blue shift of this band become more stable with respect to daylight and consequently are easier to handle. The shift of the $\pi \rightarrow \pi^*$ excitation toward shorter wave length shall be achieved by substituents introduced at the pyridine heterocycle. To study the substituent effects, excitations to the first to singlet states were calculated applying the CASPT2 approach and time dependent density functional theory (TD−DFT). The study indeed showed that electron rich substituents (like the methoxylgroup) at the positions 3, 4, and 6 of the pyridinethione heterocycle yield the desired hypsochromic shift. A free rotation of the substituent, however, is expected to quench these effects. Fluorine atoms, employed to model the influence of electron withdrawing substituents, induce also a blue shift for a substitution at the 3, 4, and 6 positions. For the multiply fluorinated molecule *N*-methoxy-3,4,6-trifluorinepyridine-2(1*H*)thione a blue shift of even 24 nm is predicted. Substituents that can conjugate with the π electrons of the heterocycle (NO_2 served as a model) only induce strong bathochromic shifts on the $\pi \rightarrow \pi^*$ excitation energy and therefore are not able to eliminate the daylight sensitivity of the precursor molecules.

Introduction

In the past years, photobiological,[1−4] mechanistic,[5,6] and synthetic investigations[7,8] were performed applying oxygen centered radicals. The first access routes to alkoxyl radicals used the homolytical O−O bond cleavage in perethers or organic peresters.[9−11] These precursor systems however are labile and difficult to handle. A newer source of alkoxyl radicals is the photochemically induced N−O bond homolysis in heterocyclic thiohydroxamic O-esters. An irradiation with near UV light leads to the liberation of the oxygen centered radicals.[12] *N*-Hydroxypyridine-2(1*H*)thione is a well-known and applied source of hydroxyl radicals.[13,14] To generate alkoxyl radicals *N*-alkoxylated pyridine-2(1*H*)thiones and thiazole-2(3*H*)thiones were developed[4,15,16] and successfully applied in synthesis.[17] Although both heterocycles serve as photochemical alkoxyl radical sources, their chemical behavior is quite different. Due to an absorption at about 360 nm, the *N*-alkoxypyridine-2(1*H*)thiones already decompose when they are exposed to unfiltered daylight. Only if the blue part of the light is filtered out are the *N*-alkoxypyridine-2(1*H*)thiones stable.[16] The *N*-alkoxythiazole-2(3*H*)thiones in contrast are stable to daylight, but when irradiated with UV light without the presence of radical trapping reagents, the yield of alkoxyl radicals is very low, and many unwanted side products are found.[12] To understand these differences, the electronic spectra and the potential energy surfaces for the photolytic N−O bond homolysis of the precursor systems *N*-methoxypyridine-2(1*H*)thione and *N*-methoxythiazole-2(3*H*)thione were computed and analyzed.[18,19] CASPT2[20,21] computations (complete active space self-consistent field calculation together with an MP2 estimation of dynamic correlation effects) assigned the spectroscopic visible absorption bands of both compounds to the $S_0 \rightarrow S_2$ transition which corresponds to a $\pi \rightarrow \pi^*$ excitation in the thiocarbonyl group of the thiohydroxamic functionality.[18] The higher stabilities of the thiazolethione compounds with respect to daylight simply result since their S_2 states are higher in energy. The higher reactivity of the alkoxyl radicals liberated after an irradiation of the thiazole compounds results from the high excess energy of the photolytic fragmentation and, as indicated by the computed potential surfaces, from a fast N−O dissociation process.[19] Due to the fast process, the excess energy is hardly distributed into vibrational or rotational degrees of freedom so that two very "hot" fragments are obtained. For *N*-alkoxypyridine-2(1*H*)-thiones the maximal excess energy of the fragments is lower and a dissipation of the excess energy is also much more likely.

For many photobiological experiments on DNA oxidation and strand-breaking processes, precursors that absorb at a wave length of about 350 nm are advantageous.[22,23] To achieve such properties, substituents were attached to the *N*-alkoxythiazole-2(3*H*)thione heterocycle to induce a red shift of the $\pi \rightarrow \pi^*$ excitation to the desired spectral region.[12,18]

However, the dissociation of the *N*-alkoxypyridine-2(1*H*)-thiones leads to a "cleaner" radical liberation process than the fragmentation of the thiazolethione precursors, so the question arises if substituents on the pyridine heterocycle can lead to a blue shift toward the desired region of about 350 nm. To get information about the influence of different substituents on the electronic spectra of *N*-alkoxypyridine-2(1*H*)thione compounds, the *N*-methoxypyridine-2(1*H*)thione heterocycle was systematically substituted by fluorine atoms, methoxyl groups, or nitro

† Dedicated to Professor Manfred Christl on the occasion of his 65th birthday.

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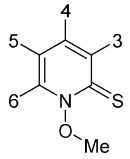

Figure 1. Numbering of the substituents on the pyridine heterocycle.

functionalities. The fluorine atoms represent a model for electron withdrawing substituents, whereas the methoxyl group is an example for an electron rich substituent. The NO_2 group is a model for substituents that are able to conjugate with the π-electron system of the pyridine heterocycle. The enumeration scheme for the substituted molecules is shown in Figure 1. The parent compound *N*-methoxypyridine-2(1*H*)thione will be abbreviated by **no**. A fluorine substituted heterocycle will be indexed by **F**, the methoxyl derivatives are indicated by an **O**, and the nitro compounds are labeled with **N**. The positions of the substituents on the heterocycle are numbered according to Figure 1, e.g. a fluorine substitution on position 3 will be enumerated as **F3**. **O346** describes the *N*-methoxy-3,4,6-(trimethoxy)pyridine-2(1*H*)thione and **N4** abbreviates *N*-methoxy-4-nitropyridine-2(1*H*)thione, respectively. The n $\rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ excitations of the parent system and the substituted molecules were calculated applying the time dependent density functional theory (TD−DFT)[24,25] in combination with the B3LYP functional.[26,27] This combination was proven to work well for this purpose. To obtain more accurate results, the fluor systems were also computed employing the CASPT2 approach. The substituent effects are explained by energy shifts of the contributing orbitals.

Theoretical Details

All DFT and TD−DFT calculations were performed with the TURBOMOLE program package.[28] For the complete active space self-consistent field (CASSCF)[29,30] and CASPT2[20,21] calculations, the MOLCAS program[31] was used.

All vertical excitation energies were computed for theoretically determined ground state geometries. The geometries of all possible fluorine- and methoxyl-pyridinethiones and the mono-nitrated molecules were obtained with the BLYP/SVP[27,32,33] approach. For these calculations, the resolution of identity (RI) approximation[34,35] together with the corresponding auxiliary basis sets[35,36] provided by TURBOMOLE were applied. This approach is sufficient since the influence of the geometry on the vertical excitation energies was found to be small in comparison to uncertainties arising from the TD−DFT approach.[19] The vertical excitation energies of the n $\rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ excitation were obtained with TD−DFT employing the B3LYP functional. In these computations, the TZVP basis sets[37] were applied. To estimate the influence of the applied geometry on the predictions of the substituent effects, the geometries of the monofluorinated molecules (**F3**-**F6**) and the most promising multiply fluorinated pyridine derivate (with respect to the desired blue shift of the $\pi \rightarrow \pi^*$ transition) were recalculated on the RI-MP2/cc-PVTZ level of theory.[38−40] For these geometries, the excitations were recalculated on the B3LYP/cc-pVTZ level of theory. Additionally the PBE0 functional[41,42] and the RICC2 approach[43,44] in combination with Dunnings triple-ζ correlation consistence basis sets were applied. The characters of the absorptions were identified through the shapes of the contributing orbitals. The energies of the first two singlet excited states of these fluorine compounds were recalculated employing the CASPT2[20,21] approach on the RIMP2/cc-pVTZ geometry. The CASSCF contained the 6 highest occupied and the 6 lowest virtual orbitals (12/12 CAS). For the PT2 computations the G3 approach[45] for the Fock matrix, and the multistate variant of the CASPT2 approach (MS-CASPT2)[46] were used. For these calculations, the cc-pVDZ basis sets were applied.[39,40] For **no** the first two excited states were also recalculated applying the cc-pVTZ[39,40] basis sets to estimate the influence of the rather small cc-pVDZ basis on the calculated excitation energies.

TABLE 1: Calculated Excitation Energies[a] for no and All Possible Substitution Patterns of the Substituted Pyridines

	X = F		X = CH_3		X = NO_2	
molecule	n $\rightarrow \pi^*$	$\pi \rightarrow \pi^*$	n $\rightarrow \pi^*$	$\pi \rightarrow \pi^*$	n $\rightarrow \pi^{*b}$	$\pi \rightarrow \pi^{*b}$
no	448	372[c]				
X3	454	360	449	350	542	461
X4	425	366	403	353	654	520
X5	472	392	463	388	515	431
X6	444	359	439	355	620	534
X34	432	355	430	363		
X35	472	376	452	374		
X36	452	351	439	354		
X45	445	380	432	380		
X46	423	349	409	352		
X56	463	379	454	397		
X345	447	367	438	363		
X346	432	343	429	352		
X356	469	370	448	375		
X456	439	365	410	357		
X3456	445	358	425	376		

[a] The TD-B3LYP/TZVP//RI-BLYP/SVP method was used. All value are in nm. [b] Due to the contributions of the nitro substituents the shape of the lowest π^* orbital differes considerably from the π^* orbitals of the other observed compounds. [c] The UV/vis spectra of no shows a broad band at about 360 nm that is assigned to the $\pi \rightarrow \pi^*$ excitation.

Results and Discussion

Since the **no** absorbs light at about 360 nm, the desired substituent effect on the spectra of the pyridine compounds would be a blueshift of the visible $\pi \rightarrow \pi^*$ excitation. The calculated excitation energies for the parent compound **no** and all investigated substitution patterns of *N*-methoxypyridine-2(1*H*)thione are summarized in Table 1.

Electron Withdrawing Fluorine Substituents on the Pyridine Heterocycle. The first two columns of Table 1 show the calculated values for the spectroscopic forbidden $n \rightarrow \pi^*$ excitation and the allowed $\pi \rightarrow \pi^*$ excitation of the fluorinated compounds. Both blue and red shifts with respect to the parent compound are predicted. For the forbidden $n \rightarrow \pi^*$ excitation, a fluorination at C_4 leads to a decrease of the excitation wave length by about 23 nm, whereas from a substitution at C_5, a red shift of 24 nm results. Almost no effects are predicted for a fluorination at C_3 or C_6. For the $\pi \rightarrow \pi^*$ excitation, which represents the initial excitation for the photochemical N−O bond homolysis, a fluorination at C_5 gives a red shift of about 20 nm, whereas the substitution at all other positions in the pyridine ring yields the desired blue shift. The biggest hypsochromic effects with 12 and 13 nm are found for **F3** and **F6**, respectively. For a fluorination at the positions 3, 4, and 6, a blue-shifted excitation energy of 343 nm is computed; that is, a hypsochromic shift of about 30 nm with respect to the parent molecule **no** is predicted.

To get deeper information about the effects of the fluorination the energies of the n, π, and π^*orbitals were investigated in detail. A fluorination of the heterocycle leads to a stabilization of all orbitals. The n orbital is uniformly decreased in energy

TABLE 2: Comparison of the Calculated Excitation Energies[a] for no, the Monofluorinated Molecules, and F346 Obtained with Different Methodes on the RI-MP2/cc-pVTZ Geometry

method	**no**	**F3**	**F4**	**F5**	**F6**	**F346**
			n → π^*			
CASPT2[b]	402	417	383	426	401	397
RI-CC2[c]	386	393	365	403	386	376
TD-B3LYP[c]	437	439	411	464	429	411
TD-PBE0[c]	415	418	389	438	409	394
			$\pi \rightarrow \pi^*$			
CASPT2[b]	374	369	364	401	363	350
RI-CC2[c]	339	331	326	361	331	316
TD-B3LYP[c]	368	352	360	390	349	330
TD-PBE0[c]	354	341	345	377	338	320

[a] All value are in nm. [b] The cc-pVDZ basis sets were used due to hardware and software limitations. [c] The cc-pVTZ basis sets were used.

(−0.16 to −0.19 eV), independent of the position of the fluorination. The π orbital is especially stabilized in molecule **F4** (−0.21 eV), whereas a C_5 fluorination leads only to a small decrease in energy of this orbital (−0.13 eV). The virtual π^* orbital exhibits the strongest stabilization in molecule **F5** (−0.33 eV).

Since the n orbital is lowered uniformly in energy, the variations of the n → π^* excitation energies result from by the energy shift of the π^* orbital. The strong stabilization of the virtual π^* orbital by a fluorination on C_5 directly reflects in the decrease of the n → π^* excitation energy in all corresponding derivatives. A comparison of the substituent effects calculated via the excitation energies ($E_{n\rightarrow\pi^*/\mathbf{Fx}} - E_{n\rightarrow\pi^*/\mathbf{no}}$) with the obtained substituent effects from the orbital energy differences ($E_{n\rightarrow\pi^*/\mathbf{Fx}} - E_{n\rightarrow\pi^*/\mathbf{no}}$) gives a standard deviation of only $\sigma_{\Delta n-\pi^*} = 0.071$ eV. For the $\pi \rightarrow \pi^*$ excitation, the substituent effects on the excitation energies are not reflected that well in the orbital energy differences. Although the decrease of the excitation energy in the case of a fluorination at C_5 is found in the corresponding orbital energy differences, the increase of the excitation energy in the case of a fluorination at C_3 and C_6 is not seen in the $\pi-\pi^*$ orbital energy differences.

To check the reliability of the TD-B3LYP method for the description of the substituent effects, excitations to the first two singlet states of the mono fluorinated pyridinethione derivates were recalculated on the CASPT2/cc-pVDZ[47] level of theory using RIMP2/cc-pVTZ geometries. This approach was found to be a reliable method to describe the spectra of the pyridinethione compounds.[19] Also the RICC2/cc-pVTZ approach on the same geometry was applied to investigate the substituent effects. A recalculation of the electronic excitations on the TD-B3LYP/cc-pVTZ and TD-PBE0/cc-pVTZ levels of theory on the RIMP2/cc-pVTZ geometry gives information about the influence of the applied geometry, basis sets, and functional on the substituent effects predicted by TD−DFT. The **F346** was also recalculated since it exhibits the biggest blue shift for the important $\pi \rightarrow \pi^*$ excitation.

The results are summarized in Table 2. The rows CASPT2 show that the more accurate "complete active space" calculations generally confirm the substituent effects for the more important $\pi \rightarrow \pi^*$ excitation but the computed shifts are smaller. For the most promising multifluorinated pyridine derivate **F346**, CASPT2 predicts a blue shift of only 24 nm (TD−DFT 30 nm) to 350 nm. The RICC2 method generally gives larger singlet excitation energies than the CASPT2, but the computed trends compare well with those predicted by the CASPT2. For the TD−DFT calculations, the differences in the substituent effects between the RI-BLYP and the RI-MP2 geometry can be seen by comparing the rows B3LYP in Table 2 with the corresponding values in Table 1. These differences are smaller than 10 nm and fall in the range of the usual uncertainties of the TD−DFT method. A comparison of the rows labeled B3LYP and PBE0 in Table 2 shows that the predicted substituent effects are less dependent on the choice of the functional than the absolute values of the excitation energies.[19]

Electron Rich Methoxyl Substituents on the Pyridine Heterocycle. To study the applicability of electron rich substituents to obtain our goal (blue shift of the $\pi \rightarrow \pi^*$ absorption band by about 20 nm), the pyridine heterocycle was also systematically substituted by methoxyl groups. The results from the TD-B3LYP calculations on the first two singlet excitations of the various possible methoxylpyridinethiones are summarized in the second set of columns in Table 1. An attachment of a methoxyl group at C_3 or C_6 has, like a fluorine substituent, almost no influence on the n → π^* excitation energy. A methoxyl group at C_4 increases the excitation energy of this transition by about 45 nm. A methoxylation at C_5 of the heterocycle has the opposite effect. It decreases the n → π^* excitation energy by 15 nm. The effects of methoxyl groups on the spectroscopic important $\pi \rightarrow \pi^*$ transition also show the same trends like the electron withdrawing fluorine molecules, but the hypsochromic effects are stronger. A methoxylation at C_5 yields a red shift of 16 nm, whereas substitutions at all other positions of the pyridine ring give quite strong blue shifts of 17−22 nm. These strong hypsochromic effects of a methoxylation at C_3, C_4, and C_6 are only found if the OMe substituent lies in the plane of the pyridine heterocycle. If the methoxyl group is twisted out of this plane, the substituent effects are quenched. Since the methoxyl groups exhibit a free rotation around the C_{ipso}−O bond the overall effect on the UV/vis spectra would be a broadened absorption band with a much smaller shift. This behavior was already found for substituents on the thiazolethione heterocycle.[18] This is also the reason why in contrast to the fluorination a multiple methoxylation yields no further hypsochromic shift. The steric demand of the methoxyl groups hinders them in their optimal orientation. For multiple methoxylated pyridinethione, a broadened absorption band with a hypsochromic shift comparable to the monomethoxylated pyridinethiones **O3**, **O4**, and **O6** should result.

To obtain information about the correlation of the orbital energy differences with the excitation energies the influence of methoxyl substituents on the orbital energies is studied. The methoxylation of **no** leads to a general increase of the orbital energies of the n, π, and π^* orbitals, independent of the position of the methoxyl group. For the n → π^* transition, the effects on the excitation energies of the molecules correlate very good with the effects on the energy differences of the contributing orbitals. The decrease in excitation energy of the n → π^* transition found for a C_5 methoxylation is rationalized with the vanishing effect on the energy of the π^* orbital (only +0.02 eV), whereas the strong increase in the excitation energy (C_4 substitution) results from its strong destabilization. The small shifts for the C_3 and C_6 substitution result since both orbitals are similarly shifted. Shifts in the orbital energy can explain the variations in the $\pi \rightarrow \pi^*$ excitation energies only for the 4- and 5-substituted systems. Like for the fluorinated pyridinethiones, the substituent effects in molecules **O3** and **O6** are not accompanied by similar shifts in the orbital energy differences.

NO_2 Substituents that Can Conjugate with the π Electrons of the Heterocycle. The last type of substituents that can influence the electronic spectra of the pyridinethione heterocycle

are functional groups that are able to conjugate with the π-electron system. An example for this kind of substituent is the nitro group. The last two columns of Table 1 list the calculated excitation energies for **no** and the mono nitro compounds **N3** to **N6**. A comparable assignment to the $n \rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ transitions could not be made due to the NO_2 contributions to the π^* orbitals. The resulting π^* orbitals differ considerably to the shapes of the π^* orbital of **no** and the fluorinated and methoxylated pyridine derivates. The π^* orbital of the nitrated heterocycles exhibit a strong stabilization (-1.02 to -1.70 eV) due to the conjugation with the NO_2 substituent which leads to a direct decrease of all excitation energies independent of the position of the NO_2 substituent. The strong bathochromic effect of the NO_2 group on the spectroscopic active $\pi \rightarrow \pi^*$ excitation leads to colored compounds and therefore to a strong sensibility to daylight which is opposite to our present goal. Nevertheless, if *N*-alkoxypyridine-2(1*H*)-thione compounds with considerably red-shifted spectra are wanted, the NO_2 group would be an appropriate substituent.

Conclusions

N-Alkoxypyridine-2(1*H*)thiones are valuable alkoxyl radical precursors; however, due to their instability in daylight, they are difficult to handle. Since this instability results from an excitation around 360 nm assigned to the $\pi \rightarrow \pi^*$ excitation, the present work tries to identify a substitution pattern which induces a blue shift of this band to about 350 nm. For this purpose, the $\pi \rightarrow \pi^*$ excitations of substituted *N*-methoxypyridine-2(1*H*)thiones were computed employing TD−DFT and the CASPT2 approach. Fluorine was taken as the electron withdrawing substituent, whereas a methoxy group serves as a model for electron donating substituents. The computations show that a mono fluorination is not sufficient to achieve the goal. The strongest hypsochromic shift is predicted for *N*-methoxy-6-fluorinepyridine-2(1*H*)thione (**F6**) with 11 nm (CASPT2). However, the effects seem to be additive. As a consequence for the *N*-methoxy-3,4,6-trifluorinepyridine-2(1*H*)thione (**F346**), a blue shift of 24 nm is predicted. The blue shifts mainly result since the π^* orbital is less stabilized than the π orbital. The electron-donating group OMe seems to lead to even stronger blue shifts of the $\pi \rightarrow \pi^*$ excitation (e.g., 22 nm for the *N*-methoxy-3-methoxypyridine-2(1*H*)thione (**O3**)). However, the overall effect will be much smaller since the strong hypsochromic effect is only found if the methoxyl group lies in the plane of the pyridine heterocycle. For an orthogonal orientation, the effect is quenched, so that for a freely rotating OMe group the effect will be smaller. For multiple methoxylations, no additivity is found, since the steric demands of the OMe groups prevent their optimal orientation. The hypsochromic effect of the methoxyl group mainly results since the π^* orbital is more destabilized than the π orbital. As a model for substituents with mesomeric effects, the NO_2 group was used. It induces only strong red shifts (160 nm for the *N*-methoxy-6-nitropyridine-2(1*H*)thione (**N6**)), which will be diminished by the rotation of the NO_2 group as it was found for OMe. The strong bathochromic shifts result since the coupling between both π systems lead to a new π^* orbital which is much lower in energy than the π^* orbital of the parent system. For the forbidden $n \rightarrow \pi^*$ excitation similar trends than for the $\pi \rightarrow \pi^*$ excitation are found.

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Supporting Information Available: RI-BLYP/SVP geometries (Cartesian coordinates) and energies of all molecules. TD−DFT B3LYP/TZVP energies of the ground and the first two excited states of all molecules. RIMP2/cc-pVTZ geometries (Cartesian coordinates) and energies of **no**, **F3-6**, and **F346**. B3LYP/cc-pVTZ, PBE0/cc-pVTZ,RICC2/cc-pVTZ and 12/12 MS-CASPT2/cc-pVDZ energies of the ground state and the first two singlet excited states of **no**, **F3-6**, and **F346**. MS-CASPT2/cc-pVTZ energies of the ground state and the first two singlet excited states of **no**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(47) To estimate the effect of this rather small basis sets on the calculated energies of the excited states, for *N*-methoxypyridine-2(1*H*)thione (**no**) these states were also recalculated with the cc-pVTZ basis sets. If the multistate variant of the CASPT2 approach (MSCASPT2) and the G3 approach[45] for the fock matrix is used the calculated excitation energies for the first two states only differ by about 0.05 eV.