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Synthesis, electronic structure and spectroscopy of bridged pyrene-$(CH_2)_n$-aryl azide systems

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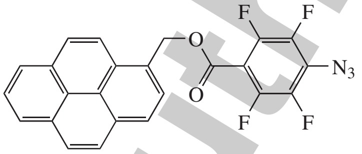
The bridged systems containing pyrenyl and aryl azido residues have been synthesized for the first time, and the quenching of pyrene fluorescence on a picosecond time scale has been observed.

The photoaffinity labeling of biopolymers[1,2] is used to obtain information on the higher order structure of RNA and RNA–protein complexes.[3,4] However, the aryl azido derivatives of nucleic acids demonstrate sometimes low specificity and cross-linking efficiency.[3] Binary reagents were proposed to increase the specificity of nucleic acid sequences.[5] These systems consist of two tandem oligonucleotides that are complementary to a target sequence of nucleic acids. Each oligonucleotide is covalently linked through its terminal phosphate group with photoreactive or photosensitizing groups. Anthracene, pyrene and perylene derivatives are used as sensitizers, and fluoro-substituted phenylazides are used as photoreagents in binary systems.[5,6] The reaction mixture is irradiated with light, which is not absorbed by aryl azide. Nevertheless, the azido group undergoes photodecomposition and forms a cross-link with protein either in or at the active site.[7] However, the mechanism of sensitization remains unknown.

Recently,[8] the quenching of pyrene fluorescence by aryl azides, including 4-azido-2,3,5,6-tetrafluorobenzoic acid **1**, has been studied in solution using fluorescence spectroscopy and nanosecond laser flash photolysis. The formation of the pyrene cation was not detected, and quenching by energy transfer was proposed.[8] However, electron transfer followed by fast N–N bond dissociation and charge recombination could not be excluded. Bonding donor and acceptor residues will facilitate the quenching and make it possible to distinguish between electron and energy transfer mechanisms. Therefore, we have performed the synthesis of bridged 1-[(4-azido-2,3,5,6-tetrafluorobenzoyloxy)methyl]pyrene **2** and 1-[3-(4-azido-2,3,5,6-tetrafluorobenzoyloxy)propyl]pyrene **3**.

Pyrene derivatives **2** and **3** were synthesized using esterification of azidotetrafluorobenzoic acid **1**[9] by pyren-1-ylmethanol **4**[10] and 3-(pyren-1-yl)propan-1-ol **5**,[11] respectively. The preparative one-stage synthesis of esters from carboxylic acids and alcohols in the presence of Et_3N was promoted by 1-methyl-2-chloropyridinium iodide **6** (Mukaiyama reagent).[12,13] The advantage of this method (Scheme 1) is the absence of acidic catalysts and the ambient temperature of synthesis, which is important for very reactive and labile azido-derivatives.[14]



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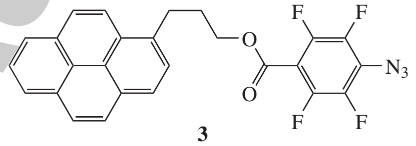

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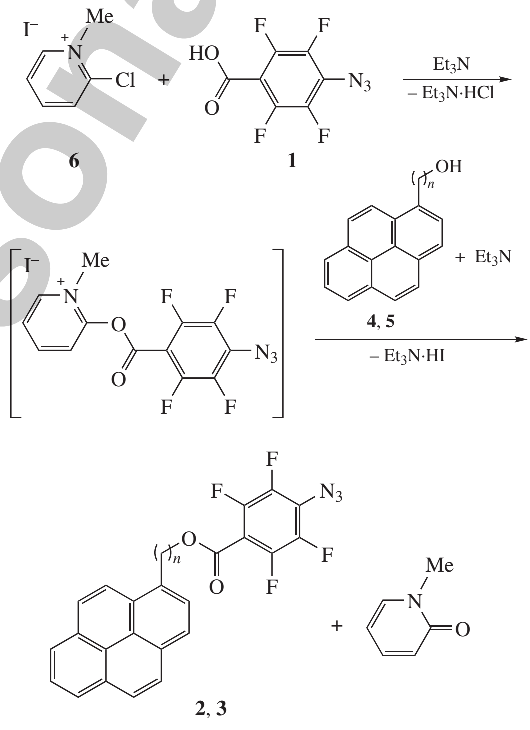

2, **4** $n = 1$
3, **5** $n = 3$

Scheme 1

The esterification of pyrenylmethanol **4** at room temperature was completed in 4.5 h. The esterification of **5** proceeded more slowly and was completed in 46 h. After chromatographic purification on silica gel and subsequent crystallization, the yields of **2** and **3** were 58 and 42%, respectively.†

The structures of esters **2** and **3** were confirmed by high-resolution mass spectrometry, ^1H NMR and IR spectroscopy. The intense peaks of molecular ions at *m*/*z* 449 and 477 were detected in the mass spectra of **2** and **3**, respectively. The

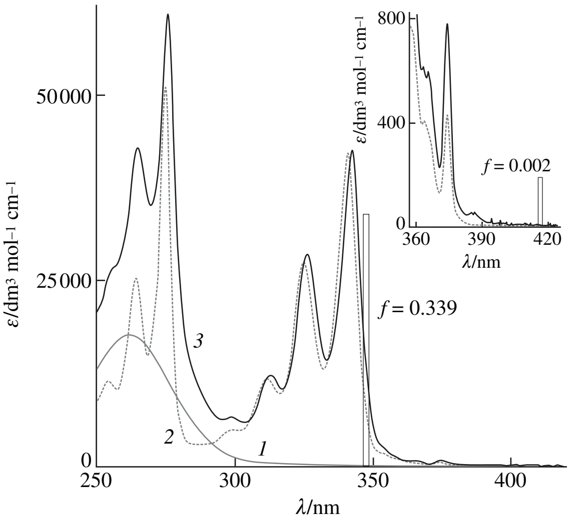

Figure 1 UV-VIS spectra of (*1*) aryl azide **1**, (*2*) pyren-1-ylmethanol **4** and (*3*) bridged system **2** in MeCN at room temperature. The calculated long wavelength transitions in the spectrum of **2** are depicted as open bars.

^{1}H NMR spectra of **2** and **3** consist of the signals typical of both pyrene and methylene protons. However, the signals of CH$_2$O protons are shifted to the lower field as compared to those of the same protons of pyrene alkanols **4** and **5** by ~0.8[15] and ~0.7 ppm,[11] respectively. The IR spectra of **2** and **3** demonstrate the presence of intense absorption bands of azido (~2120 cm^{-1}) and ester (~1720 cm^{-1}) groups.

Figure 1 demonstrates that the electronic absorption spectrum of bridged compound **2** is very close to the sum of the spectra of pyrenylmethanol **4** and azide **1**,[‡] although the maxima of the vibrational progression of **2** are slightly (1.5 nm) shifted to the red region. The difference in the spectra of **2** and **4** is more pronounced at the red edge (Figure 1, insert). Note that aryl azide **1** has no noticeable absorption at this spectral region.

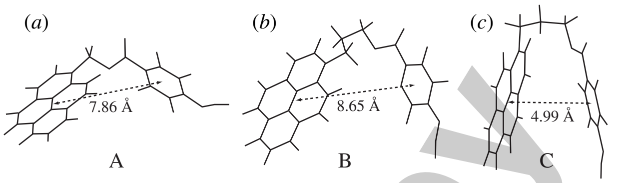

Figure 2 Structures of (*a*) the lowest energy conformer of **2** (A) and (*b*), (*c*) two low-energy conformers of **3** (B, C) optimized using B3LYP/6-31G(d) method.

A set of minima, corresponding to different conformations, were localized[§] at the potential energy surface (PES) of **2**. Figure 2(*a*) shows the structure corresponding to a global minimum on the PES. According to the calculations,[§] pyrenylmethanol **4** has a long wavelength transition at 347 nm ($f = 0.317$), while bridged compound **2** [Figure 2(*a*)] has, besides a similar band at 348 nm ($f = 0.339$), the transition at 417 nm with a very low intensity ($f = 0.002$). This transition involves electron excitation from the HOMO localized at the pyrene fragment to LUMO localized at the aryl azide fragment (Figure 3). Therefore, this excited state is the charge-transfer (CT) state. The contribution of this transition to the spectrum of **2** could explain the above distinction at the red edge of the spectra (Figure 1, insert). Note that taking into account the solvent using the PCM model[16] has a minor effect on transitions and shifts the latter to the blue region (408 nm in MeCN).

High-level RI-CC2 calculations,[17] as well as early semi-empirical ones,[18,19] predict that the first excited singlet states (S$_1$) of phenyl azide and its simple derivatives [best characterised as π → (in plane, π*, azide) excitations] are dissociative toward the formation of molecular nitrogen and the singlet nitrene. Usually, these $S_0 \rightarrow S_1$ transitions manifest themselves as weak long asymmetric tails,[8,20] which is typical of the excitation to the dissociative states. According to our calculations,[§] the $S_0 \rightarrow S_1$ transition of azide **1** at 309 nm is also characterized as π → (in plane, π*, azide) excitation (HOMO → LUMO + 1) and has a very low oscillator strength (3×10^{-4}).

Figure 4 depicts the fluorescence decay kinetics of bridged system **2** (curve *1*).[¶] This kinetics is well described by a two-exponential function with time constants of $\tau_1 = 164\pm2$ ps and $\tau_2 = 6.9\pm0.2$ ns. The contribution of the second term is very small ($A_2/A_1 \sim 0.06$) and is, probably, due to the photoproduct. The time constant of the fluorescence decay of pyrenylmethanol **4** was measured to be 200±10 ns. Therefore, the fluorescence quantum yield of bridged system **2** is about three orders of magnitude as low as that of **4**. Thus, we failed to detect the fluorescence spectrum of **2**.

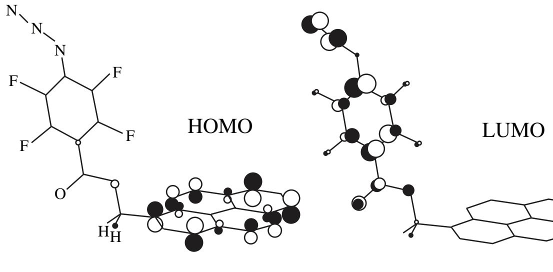

Figure 3 Frontier MOs of 1-[(4-azido-2,3,5,6-tetrafluorobenzoyloxy)methyl]-pyrene **2** calculated at the B3LYP/6-31(d) level.

[†] The ^{1}H NMR spectra of **2** and **3** were recorded using a Bruker DPX 200 spectrometer in CDCl$_3$ at room temperature. The high-resolution mass spectra were measured using a Finnigan MAT 8200 spectrometer. The IR spectra were recorded using a Bruker Vector 22 spectrometer. The course of reaction and the purity of products were controlled using TLC monitoring (Silufol UV 254; eluent, CHCl$_3$–hexane).

Synthesis of 1-[(4-azido-2,3,5,6-tetrafluorobenzoyloxy)methyl]pyrene **2**. A solution of 91 mg (0.39 mmol) of 4-azido-2,3,5,6-tetrafluorobenzoic acid **1**,[9] 93 mg (0.36 mmol) of 1-methyl-2-chloropyridinium iodide **6**,[12,13] 70 mg (0.30 mmol) of pyren-1-ylmethanol **4**,[10] and 73 mg (0.72 mmol, 0.1 ml) of Et$_3$N in 3 ml of CH$_2$Cl$_2$ was stirred under N$_2$ atmosphere at 20 °C for 4.5 h. The reaction mixture was separated by chromatography on silica gel with a CH$_2$Cl$_2$ eluent. The effluent containing **2** was evaporated *in vacuo*, the oily residue was blended with 5 ml of hexane, and the crystals were filtered off and washed with 5 ml of hexane to give 79 mg (58%) of compound **2**, which was additionally recrystallized from CHCl$_3$, mp 188–190 °C. ^{1}H NMR, δ: 6.12 (s, 2H, CH$_2$OCO), 7.95–8.40 (m, 9H). IR (CHCl$_3$, ν/cm^{-1}): 1720 (C=O), 2120 (N$_3$). HRMS, *m/z*: found, 449.07922; calc. for C$_{24}$H$_{11}$N$_3$O$_2$F$_4$, 449.07873.

Synthesis of 1-[3-(4-azido-2,3,5,6-tetrafluorobenzoyloxy)propyl]pyrene **3**. Ester **3** was synthesized and purified similar to **2**. The esterification was completed in 46 h, the yield of crystalline **3** was 42%. Compound **3** was additionally recrystallized from CH$_2$Cl$_2$, mp 150.5–152.5 °C. ^{1}H NMR, δ: 2.23–2.40 (m, 2H, CH$_2$C*H*$_2$CH$_2$OCO), 3.50 [t, 2H, C*H*$_2$(CH$_2$)$_2$OCO, *J* 7.4 Hz], 4.45 [t, 2H, (CH$_2$)$_2$C*H*$_2$OCO, *J* 6.0 Hz], 7.80–8.30 (m, 9H). IR (CHCl$_3$, ν/cm^{-1}): 1720 (C=O), 2130 (N$_3$). HRMS, *m/z*: found, 477.10970; calc. for C$_{26}$H$_{15}$N$_3$O$_2$F$_4$, 477.11003.

[‡] Electronic absorption spectra were recorded on a UV-VIS Shimadzu 2401 spectrometer. Pyren-1-ylmethanol **4**[10] was purified by chromatography (silica gel; eluent, benzene), treated with activated carbon and finally recrystallized from a benzene–hexane mixture. 4-Azido-2,3,5,6-tetrafluorobenzoic acid **1** from Aldrich was used.

[§] The geometries of **2** and **3** were optimized by the B3LYP/6-31G(d) method.[21,22] All equilibrium structures were ascertained to be minima on potential energy surfaces. The electronic absorption spectra (EAS) were calculated by the time-dependent TD-B3LYP/6-31+G(d) technique.[23] All calculations were performed with the Gaussian-03[24] suite of programs. The influence of the solvent on the EAS was taken into consideration by the PCM[16] models as implemented to Gaussian 03.

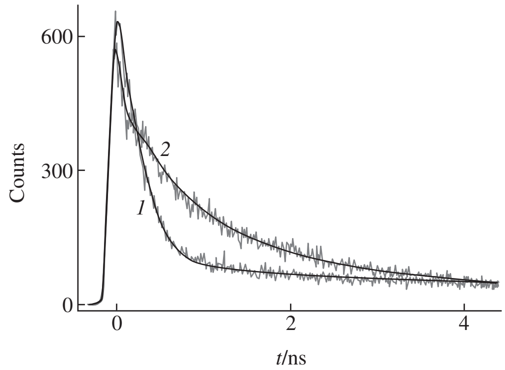

Figure 4 Fluorescence decay kinetics of bridged systems (*1*) **2** and (*2*) **3** in MeCN at room temperature (gray curves) and the best fitting by (*1*) double- or (*2*) three-exponential functions taking into account the instrument response function (black curves).

The fluorescence decay kinetics of bridged system **3** is also shown in Figure 4 (curve *2*). As compared to that of **2**, this kinetics is well described by a three-exponential function with time constants of ~40 ps, 770±20 ps and 3.8±0.5 ns. The contribution of the last term is small [$A_3/(A_1+A_2)$ ~ 0.06] and could also be due to the photoproduct.

In the case of **3**, a bigger set of conformations were localized.[§] The structures of two low-energy conformations of **3** are displayed in Figure 2(*b*),(*c*). Figure 2 demonstrates that the distance between the centers of pyrene and aryl fragments in bridged system **2** (A) is shorter than in structure B and longer than in structure C. This is consistent with kinetic results.

Therefore, the quenching of local pyrene fluorescence in bridged systems **2** and **3** is efficient and proceeds on a picosecond time scale. This quenching could also be considered as internal conversion in the combined systems. According to the calculations, the CT states of the bridged systems are lower in energy than the local excited state of the pyrene residue. Thus, quenching of the local pyrene fluorescence could be due to the conversion to the CT state. In this case, electron transfer is the mechanism of this process.

Due to the dissociative nature of the S_1 state of azide **1**, its energy cannot be precisely defined. Thus, the energy transfer to the local dissociative state of the aryl azide residue cannot still be excluded. Only direct observation of the pyrene cation formation could prove the electron transfer mechanism. Thus, a detailed investigation of the photophysics of **2** and **3** using femtosecond transient absorption spectroscopy[17] will be published elsewhere.

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[¶] The fluorescence kinetics was measured using a time-correlated single-photon counting (TCSPC) setup.[25] The picosecond pulses at 336 nm were used to excite solutions held in a 1 cm cuvette with OD ~ 0.3 at 336 nm. Fluorescence was collected at 90°, directed through a double monochromator (American Holographic), and detected by a microchannel-plate photomultiplier tube (Hammamatsu). The instrument response time was ~80 ps (fwhm). All fluorescence transients were recorded at an emission wavelength of 360–380 nm. Lifetimes were determined by iterative reconvolution of double- or three-exponential function with instrument response.

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