An exploratory and mechanistic study of the defluorination of an (aminofluorophenyl)oxazolidinone: $S_N1(Ar^*)$ *vs.* $S_{R^+N}1(Ar^*)$ mechanism

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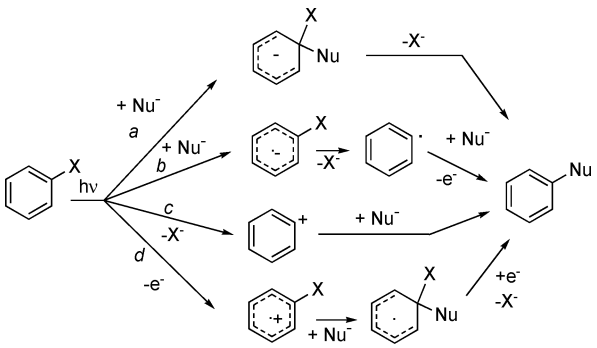
The morpholinofluorophenyloxazolidinone **1** (the antibacterial drug linezolid) is found to undergo reductive defluorination upon irradiation in water (Φ 0.33), in some of the products accompanied by the simultaneous oxidative degradation of the morpholine side chain. In the presence of chloride, iodide and pyrrole, the fluorine is substituted by these groups (with pyrrole, in position 2). The defluorination is less efficient in methanol and mainly leads to reduction (Φ 0.053). These data can be accommodated through two different mechanisms, viz. either C–F bond heterolysis to give a phenyl cation [$S_N1(Ar^*)$], or ionization to give a radical cation [$S_{R^+N}1(Ar^*)$]. Steady-state and time resolved data have been gathered for clarifying this issue. It is found that, indeed, ionization of **1** is efficient and proceeds from the singlet, but leads to no irreversible change. On the contrary, triplet ^{3}**1** (lifetime 0.5 μs in MeOH, <0.1 μs in water) fragments and gives the corresponding triplet phenyl cation. The last intermediate explains well the observed hydrogen abstraction both inter- (from the solvent, when this is reducing) and intramolecularly (from the morpholine group), as well as addition to a charged anion or to a neutral π nucleophile such as pyrrole. The rationalization is supported by the study of some related molecules. Thus, the only photochemical reaction from the non fluorinated analogue of linezolid (that ionizes just as **1**) is an inefficient degradation of the morpholine chain (Φ 0.001), while a simple model such as *N*-(2-fluorophenyl)morpholine undergoes photosolvolysis in water and is not trapped by pyrrole.

Introduction

Photochemistry has an important role in aromatic nucleophilic substitution[1] and, along with catalysis by transition metal complexes,[2] contributes to widen the scope of a class of reactions that otherwise requires harsh conditions or activating (electron-withdrawing) substituents. A number of convenient photochemical procedures for obtaining nucleophilic substitutions has been reported and include reactions characterized by good yields and mild conditions. This topic is actively pursued, in particular for the formation of an aryl–carbon bond by substitution of a phenyl halide or similar reagent by a carbon-based nucleophile. A peculiarity of photoinduced reactions is that substitution of a fluorine atom is generally viable also for *non activated* substrates (*i.e.*, those not bearing electron-withdrawing substituents).[3] In thermal chemistry, fluorine substitution is common for activated substrates, but otherwise less frequent, *e.g.* in catalytic methods, where the other halides are used more often.[4]

As for the mechanism, the photochemical substitution may occur *via* the excited state analogue of the addition elimination path typical of the ground state reactions, the $S_N2(Ar^*)$ mechanism, path *a* in Scheme 1. However, a larger number of examples pertain to the family of the $S_{RN}1$ reactions, where the key step is cleavage of the C–X bond from the radical anion (arising by photoinduced electron transfer) to form the actual reacting intermediate, the phenyl radical. Due to this characteristic, this method is generally limited to less strongly bonded aryl halides, such as iodides and bromides (path *b*).[5–7]



Scheme 1 Mechanisms of aromatic photosubstitution reactions.

A different pathway has taken a more extensive role in recent years, however, with the identification of a number of reactions that appear to proceed *via* unimolecular fragmentation of the (triplet) excited state and to form a phenyl cation as the intermediate [$S_N1(Ar^*)$ mechanism, path *c*].[1a,3,8] In this case a fluorine atom is accessible to substitution. This reaction has attracted interest both because of the smooth substitution in chlorides and fluorides and because in this way a phenyl cation is produced and this intermediate, difficult to access by non photochemical methods, has demonstrated to be a synthetically useful electrophilic reagent for the arylation of alkenes, aromatics and heteroaromatics under mild conditions. This reaction has been documented for electron-donating substituted aromatics in strongly polar media, *e.g.* for chloro- or fluoroanilines, phenols and (thio)anisoles in alcohols, acetonitrile or aqueous mixtures.[3] It has

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been further identified for some terms of an important family of drugs, that of fluoroquinolones.

Mechanistic and computational investigations have been carried out and support for the involvement of path *c* has been obtained through several pieces of evidence.[8] However, the characteristics of the reaction, at least as presently known, viz. the limitation to electron rich substrates and highly polar media, suggest a further possible mechanism, likewise initiated by a unimolecular step. Thus, it may be that in a polar solvent such easily oxidized compounds lose an electron, either by photoionization, or by electron tranfer within an exciplex ($[A\cdots A]^* \rightarrow A^{\bullet+} + A^{\bullet-}$). The radical cation thus formed adds a nucleophile leading to a neutral radical intermediate, and the halide is cleaved at this stage [$S_{R+N}1$(Ar*) mechanism, path *d*]. Such a mechanism has been invoked in some cases, indeed has been considered to be characteristic of good donors in water[9] and, although it seems in principle less appealing for the cleavage of the strong C–F bond, it deserves attention.

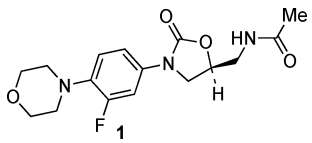
Below we report a study on the photochemistry of the antimicrobial drug linezolid, which helps in understanding the scope of nucleophilic aromatic substitution, since both paths *c* and *d* are followed, while on the other hand adds to the continuing effort from various laboratories for clarifying the photochemistry (and phototoxicity mechanism) of fluorinated drugs.[10]

Results

Linezolid pertains to the family of oxazolidinones a highly promising new class of antimicrobials[11] and is the only term of this series presently licensed for clinical use. The heterocyclic ring bears a *N*-phenyl substituent, and the latter in turn has a fluorine and a dialkylamino group as substituents.

Photochemistry

In the frame of the validation study, (*S*)-3-[3′-fluoro-4′-(*N*-morpholino)phenyl]-5-*N*-acetamidomethyloxazolidin-2-one (linezolid, **1**) has been previously irradiated in parenteral sterile preparations in citrate buffer, where compounds **3**–**5** were characterized.[12]



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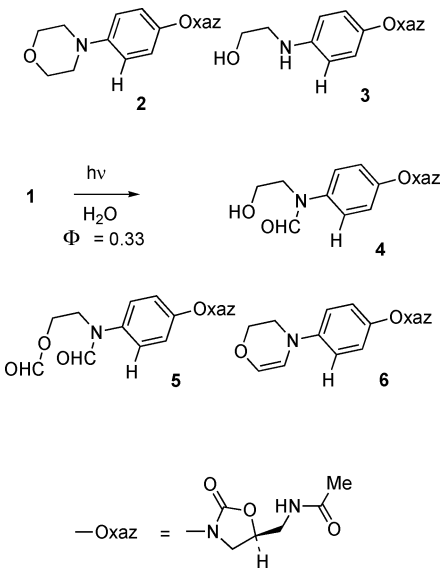
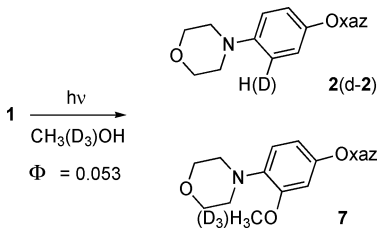
The present investigation was carried out in neat water and methanol. Irradiation of **1** (6×10^{-3} M) in nitrogen-flushed water gave several products. The main one was isolated by chromatography and shown to preserve intact the acetylaminomethyloxazolidinone moiety (Oxaz in Scheme 2) of the starting material, while the fluorine atom on the aniline ring had been substituted by a hydrogen (compound **2**, 30% yield). Two further products were isolated (**3** and **4**, together 16%) that had undergone both ring defluorination and degradation of the morpholine chain to a *N*-(2-hydroxyethylamino) group, with the difference that the latter compound bore also a *N*-formyl group. These products along with the corresponding *O*, *N*-diformyl derivative **5** (present in a small amount as indicated by HPLC/MS analysis), but not **2**, had been previously characterized from the above-mentioned irradiation of **1** in citrate buffer. The analysis showed also the presence of a



Scheme 2 Products from the photoreactions of fluorophenyloxazolidinone **1** in water.

further minor peak, with *m*/*z* 217, corresponding to that of **2** less two hydrogen atoms. This was proposed to be the corresponding dehydromorpholino derivative (**6**). Non-identified high molecular weight products were also present. Omitting degassing did not affect the product distribution, but the reaction was slowed by a factor of 3. Carrying out the irradiation in D_2O led to no significant deuterium incorporation in products **2** to **6**.

Compound **1** reacted also by irradiation in nitrogen-flushed methanol, though the process was slower, and gave defluorinated **2** as the main product (70%, see Scheme 3), along with a small amount of the methoxyphenyl derivative **7** and traces of compound **3**. A similar experiment in CD_3OH gave again **2**, which was isolated and shown to be 100% deuterated at position 3′ (product d-**2**, see Experimental). The reaction course was again similar in air, although much slower. Preliminary experiments in MeCN (N_2 or air) led to a complex product mixture and discouraged further examination.

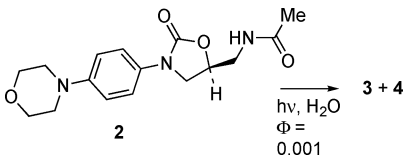


Scheme 3 Products from the photoreaction of compound **1** in methanol.

The quantum yield (Φ) of these reactions was measured in separate low conversion experiments at 280 nm. The values obtained were 0.33 in water and 0.053 in methanol.

As seen above, the processes occurring with compound **1** were defluorination and oxidative degradation of the morpholine chain. In order to explore the relation between the two processes, the photochemistry of fluorine-free **2** was examined. This compound was prepared from 4-(*N*-morpholino)-aniline following the same approach reported for **1** (see Experimental). Under irradiation,

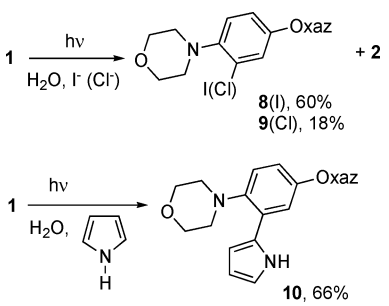
compound **2** reacted sluggishly both in water and in methanol to give products **3** and **4** (see Scheme 4). The quantum yield was quite low (*ca.* 0.001 in water and 0.0025 in methanol).



Scheme 4 Products from the photoreaction of the defluoro-analogue **2**.

The reactions observed with **1** differed from those known for 2-fluoroaniline, for which photosubstitution to give the phenol is the main process in water, and were similar to those reported for 4-fluoroaniline (and the corresponding *N*,*N*-dimethyl derivatives), which undergo reduction rather than substitution.[13] In order to understand the scope of the two reactions, we studied on one hand whether the morpholine side-chain could introduce some difference with respect to the NH_2 or the NMe_2 group and on the other we explored whether substitution reactions different from solvolysis could take place with **1**. Notice that with 4-fluoroaniline substitution of the fluorine by a halide or by a π nucleophile occur efficiently.[3]

As for the latter point, the effect of some additives on the photochemistry of compound **1** in water was examined. Thus, irradiation in 0.2 M sodium iodide solution led to the isolation of the 3′-iodo derivative **8** in 60% yield, accompanied by 19% of **2** (Scheme 5) An analogous experiment in 0.2 M sodium chloride caused a less marked change, since **2** remained the main product (45%), but HPLC/MS showed the presence of a chlorinated product, reasonably of structure **9** in *ca.* 18% yield.



Scheme 5 Photochemistry of compound **1** in water: trapping by chloride, iodide and pyrrole.

Finally, irradiation of **1** in an aqueous solution containing 0.2 M pyrrole led to a compound identified as the 3′-(2″-pyrrolyl) derivative **10** as virtually the only products (Scheme 5, isolated yield, 66%).

On the other hand, irradiation of *N*-(2-fluorophenyl)-morpholine (**11**) gave the corresponding hydroxyphenyl derivative **12** as the only isolated product. The product distribution remained unchanged in the presence of 0.2 M (as well as 1 M) pyrrole. In methanol by far the main product was phenylmorpholine **13**. Also in this case, no change in the product distribution occurred in the presence of pyrrole.

Spectroscopy

The UV absorption of linezolid in water and methanol exhibits a maximum at 252 and 259 nm respectively (log ε 4.3) and a further partially superimposed band (shoulder at *ca.* 275 nm, tail extending up to 310 nm). In the fluorine-free analogue **2** these values were slightly (5 nm) red shifted. In fact, the UV spectra of compounds **1** and **2** are quite similar to that of 2-fluoroaniline and aniline, respectively, and indeed the absorbing chromophores are centered on those moieties. As for emission, compound **2** (λ_{max} 377 nm; $\Phi_F = 0.073$ in water) fluoresced much more intensively than fluorinated **1** (λ_{max} 377 nm; $\Phi_F = 0.0004$). Also the phosphorescence in ether–pentane–alcohol glass was apparent with **2** (λ_{max} 430 nm), while it was barely detectable with **1** (λ_{max} 450 nm, *ca.* 30 times less intensive). The phosphorescence lifetime of **1** was likewise much shorter than that of **2** (5 ms *vs.* >100 ms in ether–pentane–alcohol glass at 77 K). Comparison with literature data shows that the aniline fluorescence is at 334 nm ($\Phi_F = 0.15$ in MeCN) and the phosphorescence at 405 nm (in methyltetrahydrofuran glass at 77 K),[14] with an efficient intersystem crossing in solution ($\Phi_{ISC} \approx 0.7$); 4-fluoroaniline fluoresces with a similar efficiency ($\Phi_F = 0.12$ in MeCN).[15]

Transient spectroscopy

Laser flash photolysis was then used searching for intermediate(s). Actually, flashing a nitrogen-flushed 1×10^{-4} M solution of **1** in water caused the appearance of a transient absorption extended over a large wavelength range (from 270 to over 600 nm, see Fig. 1a), with a further absorption centered at 700 nm (shown enlarged in Fig. 1b). When a solution saturated with N_2O (a known trap for free electrons) was flashed, the red end portion of the transient was eliminated (see inset in Fig. 1b), while the remaining part was unaffected. This had a lifetime of *ca.* 70 μs and underwent only a small quenching (by a few percent) in an oxygen-equilibrated solution. On the other hand, flashing in methanol gave similar results, but now a short-lived component could be identified in the 300 nm region (lifetime *ca.* 0.5 μs, 2nd order decay, see Fig. 2), which was barely discernible in the spectrum in water. This short-wavelength part was completely quenched in an oxygen-flushed solution, as expected for a triplet.

Most notably, quite similar transients in terms both of the spectrum shape and of lifetime were observed when the fluorine-free morpholinophenyloxazolidinone **2** was flashed (not reported).

Electrochemical measurements

The detection of free electrons suggested that photoionization was occurring and support was seeked by cyclic voltammetry. With an aqueous solution of **1**, two anodic waves were detected (see Fig. 3). The first one corresponded to a reversible, monoelectronic oxidation (E° = +830 mV *vs.* SCE, average from three measurements at different scanning rates), the latter to an irreversible wave. This corresponded to a bielectronic (as deduced from the E_p *vs.* scanning rate plot) oxidation (E° *ca.* 1100 mV *vs.* SCE). A similar examination of fluorine-free **2** (E° = 680 mV *vs.* SCE) and of fluorophenylmorpholine **11** gave very similar results.

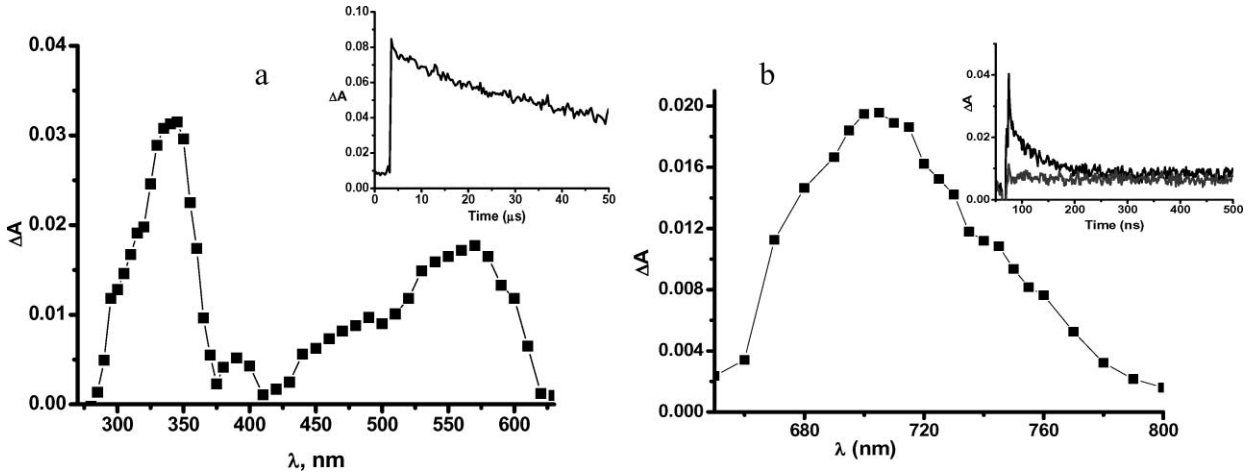


Fig. 1 Difference absorption spectrum of a 1×10^{-4} M solution of **1** in water 0.5 μs after flashing at 266 nm. (a) Spectrum in the 270–620 nm region. Inset: decay of the absorption at 340 nm. (b) Spectrum in the 650–800 nm region (different scale). Inset: decay of the 675 absorption in the nitrogen flushed (upper trace) and nitrogen oxide flushed (lower trace) solution.

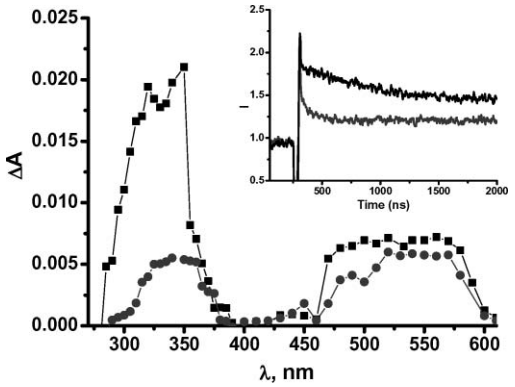


Fig. 2 Difference absorption spectrum of a 1×10^{-4} M solution of **1** in methanol 0.5 μs after flashing at 266 nm: upper trace, nitrogen-flushed solution; lower trace, oxygen-flushed solution. Inset: decay of the absorbance at 310 nm in a nitrogen (upper trace) and oxygen-saturated (lower trace) solution.

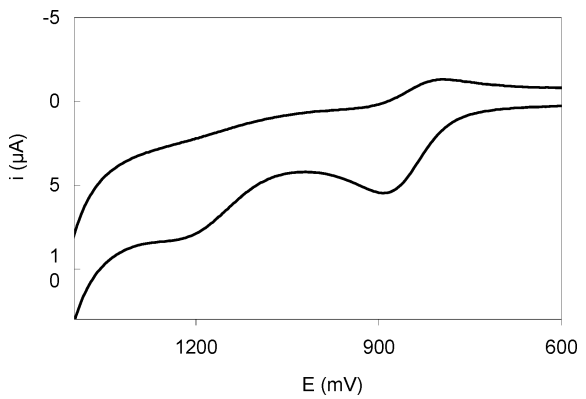
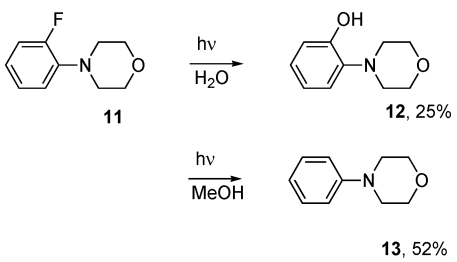


Fig. 3 Cyclic voltammogram of **1** (1.5×10^{-3} M in water, 1.2 V min^{-1}, KCl 0.1 M as supporting electrolite).

Discussion

The above results show that reductive defluorination, accompanied or not by reaction at the morpholine moiety, is the main process from the fluorophenylmorpholine derivative linezolid (**1**) in water or methanol. Homolytic cleavage of the C–F bond is excluded because the energy of both singlet (E_S 84 kcal mol^{-1}) and triplet (E_T 75 kcal mol^{-1}) states were too low to make this ($E_{Ar\text{-}F}$ *ca.* 120 kcal mol^{-1}) a viable path. For the same reason, the $S_{RN}1$ mechanism (path *b* in Scheme 1) is discarded.

As for the addition–elimination mechanism $S_N2(Ar^*)$, path *a* in Scheme 1, this can be excluded on the basis of the product distribution, since if this were involved, a nucleophilic solvent such as an alcohol or water would substitute the fluorine atom. Solvolysis is indeed the main process with *N*-(2-fluorophenyl)morpholine (**11**) which gives the phenol **12** in water (although reduction to **13** is the main process in methanol, see Scheme 6), analogously to what was previously observed with 2-fluoroaniline,[16] but contrary to the case of **1**, where no phenol is formed in water and only a minor amount of the methoxyphenyl derivative is formed in methanol. Thus, the morpholine group *per se* does not introduce a difference in the photochemistry of fluorobenzenes with respect to other amino substituents. Apparently, the presence of the oxazolidinonyl group as a further donating substituent determines the peculiar chemistry observed with **1**, for which two rationalizations remain, viz. either monomolecular fragmentation of the excited state to yield the phenyl cation or photoionization (paths *c* and *d* in Scheme 1).



Scheme 6 Photochemistry of 2-fluorophenylmorpholine.

There is no doubt that ionization occurs, as conspicuously shown by the flash photolysis experiments. The characteristics of the observed transient, extended over most of the visible, that

is the long lifetime and the minimal oxygen effect, excluded that this was an excited state or a radical, while were well compatible with an ionic intermediate. Indeed, the transient spectrum shown in Fig. 1a was closely similar to that of the radical cations of *N*,*N*-dimethylaniline (Wurster blue) and of *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylendiamine (two intense bands at 320 nm and at 530–640 nm).[17] This transient can thus be safely attributed to the radical cation $\mathbf{1}^{\bullet+}$ formed through a photoionization process according to eqn (1).

$$\mathbf{1} + h\nu \rightarrow \mathbf{1}^{\bullet+} + e^- \quad (1)$$

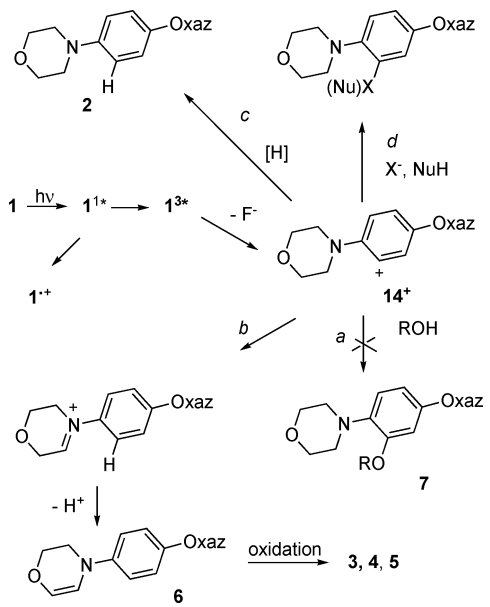
The electron ejected was indeed detected farther to the red with respect to the previous transient (see Fig. 1b), and the identification was confirmed by the selective quenching of that part of the spectrum by N_2O. If one assumes that the molar absorptivity of $\mathbf{1}^{\bullet+}$ is similar to that of Wurster blue (ε_{565} 12 500 mol^{-1} cm^{-1}),[17] then the quantum yield of formation of this species is *ca.* 0.25.

The flash photolysis evidence fitted with the electrochemical results, showing that single electron oxidation of **1** was possible under mild conditions and involved the aniline moiety (compare model compound **11** and *N*-phenylpiperidine that are oxidized at 0.95 V *vs.* SCE,[18] respectively, while non phenylated oxazolidinones are oxidized at a much more positive potential, *ca.* 2.4 V *vs.* SCE).[19] The excited state involved in the photoionization was the singlet, as indicated by the lack of oxygen effect in the formation of $\mathbf{1}^{\bullet+}$. Importantly, fluorine-free **2** gave a transient absorption closely similar to that observed with **1** both in shape and in lifetime (and likewise not affected by oxygen). This again supported the attribution of the radical cation structure to the transient from **2**, just as that from **1**, since ionization appeared to be the only conceivable phenomenon both of the two compounds, of almost identical oxidation potential, may undergo, with the further proviso that electron ejection had to be reversible, since **2** was virtually photostable. The above evidence excluded that these transients were involved in the observed photochemical defluorination of **1**, because otherwise the transient from this compound should be much shorter-lived than that from **2**, as the former reacts almost 100 times more efficiently than the latter in water.

Excluding ionization (path *d* in Scheme 1) left excited state fragmentation (path *c*) as the viable mechanism for defluorination. The conspicuous ionization made it unlikely that this was a competitive process from the singlet. Moreover, a direct indication came from flash photolysis in MeOH, where besides the intense signal of $\mathbf{1}^{\bullet+}$, a shorter-lived transient was observed at 280–320 nm. This was diffusion-controlled quenched by oxygen (see Fig. 2, inset) and had no analogy in water, where a transient in that region was barely detected with a short time delay. These pieces of evidence supported the assignment of the part of the transient around 300 nm to triplet $\mathbf{1}^{3}$* that fragmented six times more efficiently in water than in MeOH and thus was much shorter-lived in the former solvent. This fact, together with the increased intensity of the radical cation, made the triplet all but undetectable in the latter solvent. A triplet path was also supported by the remarkably decreased phosphorescence lifetime observed with **1** in comparison to **2**, indicating that a further process involving the fluorine atom was competing with emission. The behavior is analogous to that of 4-fluoroaniline, where calculations on the triplet state[20] showed that heterolysis of the C–F bond was endoergonic in polar/non protic solvents, but became exergonic in the presence of water (see eqn (2)) due to the determining contribution of the formation of the H–F bond. It is thus understandable that the photoreaction is more efficient in water than in methanol, since the former is both a more polar (ε 80.2 *vs.* 32.6) and a slightly more acidic solvent. As a result, heterolysis according to eqn (2) is exclusive in water, while in MeOH solvolysis contributes to some degree (see below).

$$Ar\text{-}F + h\nu + H_2O \rightarrow Ar^+ + HF + OH^- \quad (2)$$

The triplet path is supported by the marked deceleration of the photoreaction under air, the quenching of the $^3\mathbf{1}$ in methanol and the chemistry observed, which well corresponds to that of a phenyl cation in the triplet state, the expected first intermediate from the cleavage of $^3\mathbf{1}$ and presumably the ground state of this species analogously to the 4-aminophenyl cations[13,21] (see intermediate $\mathbf{14}^+$ in Scheme 7). There is now plentiful indication of the contrasting reactivity of singlet and triplet phenyl cations, both from experiments and from computation.[22] Thus, triplet phenyl cations are not quenched by O_2 (and indeed the product distribution is unchanged) and form a complex with, but do not add to, a neutral n donor such as water because in such intermediates the charge is dispersed on the ring ($\pi^5\sigma^1$ structure) and is negligible at C_1, contrary to what happens in the singlet ($\pi^6\sigma^0$ structure, charge localized at C_1).[13,21,23] On the other hand, both singlet and triplet cations react with π-nucleophiles and with charged n nucleophiles.



Scheme 7 Mechanism for the intra- and intermolecular reaction of compound **1**.

The photoreactions of linezolid (see Scheme 7) can thus be attributed to triplet cation $\mathbf{14}^+$. In methanol, the main path is intermolecular hydrogen abstraction (path *c*) leading to compound **2**, for which the role of hydrogen abstraction from the solvent is demonstrated by the formation of 3′-d **2** in CD_3OH. Ether **7** is a minor product and arises *via* either a minor path from $\mathbf{14}^+$ or solvolysis directly from the excited state.

Another possibility for the cation is intramolecular hydrogen abstraction from the vicinal alkylamino group. In the present cases, this kind of process is revealed in non-hydrogen donating water by formation of products **3** to **6**, where the morpholine group is stepwise oxidized. This process can be rationalized *via* deprotonation of the cation to form enamine **6** (path *b*, Scheme 7) and subsequent hydrolysis as well as further oxidation yielding products where a more deep degradation of the side chain has occurred (such as products **3** to **5**). The oxidation of the morpholine group had been recognized in the above-mentioned photostability studies on **1**,[12] but the connection with defluorination had not been explicitly recognized.

This process is closely analogous to that observed with fluorinated heterocycles bearing an alkylamino side-chain, such as fluoroquinolones orbifloxacin[24a] and lomefloxacin (when in the anionic form).[24b] In that case, reductive defluorination is accompanied by oxidative degradation (to a various degree) of the dialkylamino side chain (a piperazine ring). It clearly differs, on the other hand, from the mere degradation of the morpholine group in non-fluorinated anilines, as observed here in the case of **2**. The latter process occurs with a much lower quantum yield (300 times lower than that of **1** in water). This implies that secondary oxidation of **2** gives no major contribution to the formation of products **3** to **6** from **1**, which are likely formed in a monophotonic reaction.

The photochemical reaction of **2** is an instance of the oxidation of alkyl groups in *N*-alkylanilines, a common process with this class of compounds.[25] This generally involves electron transfer to an excited state or a photochemically formed radical and is quite inefficient, *e.g.* occurring with $\Phi \approx 1 \times 10^{-3}$ with fluoroquinolones that do not undergo defluorination, such as ofloxacin[10a] and rufloxacin,[26] exactly as it is the case with compound **2**.

While water and methanol have no effect, a π nucleophile such as pyrrole is an effective trap and diverts the reactivity of a strong electrophile such as cation $\mathbf{14}^+$ (path *d*). Selective arylation in position 2 of electron rich heterocycles had been previously observed upon photolysis of 4-chloroaniline in organic solvents.[22] Furthermore, the cation is trapped by charged nucleophiles. The soft iodide is by far a better trap than chloride, again an indication of the non-localized nature of cation $\mathbf{14}^+$.

To summarize, the observed photochemistry with **1** is strictly analogous to that of 4-fluoroaniline (reductive defluorination and fluorine substitution by halides and by π-nucleophiles) and differs from that of 2-fluoroanilines, as confirmed here for the case of 2-fluorophenylmorpholine **11**, where solvolysis of fluorine is observed and the conspicuous photoionization has no role in the defluorination.

Conclusion

In conclusion, linezolid is highly photoreactive in water and to a lesser degree in methanol. This compound offers the possibility of comparing two mechanisms for aromatic photosubstitution, viz. $S_{R^+N}1(Ar^*)$ and S_N1 (Ar^{3*}). The latter one is indicated by the fact that ionization occurs (from the singlet) but causes no irreversible decomposition, while the reactions observed (inter- and intramolecular hydrogen transfer, trapping by halide ions and by pyrrole) are all compatible with a triplet phenyl cation as the intermediate. This finding extends what has been found with other families of fluorinated electron-rich (hetero)aromatics (besides anilines, anisoles[27a] and indoles)[27b] that likewise undergo smooth substitution *via* unimolecular fragmentation from the triplet. The peculiar chemistry of the resulting cation (H abstraction or insertion in a C–H bond, addition to π nucleophiles) might find some preparative application, *e.g.* for selective arylation reactions, as here with pyrrole, with the advantage of a favorable route in an eco-friendly solvent such as water.

On the other hand, the frequent occurrence of the fluoroaniline motif in widely used drugs prompts attention to photolability and phototoxicity of such derivatives.[28] Virtually all of the oxazolidinone drugs bear an aminofluorophenyl substituent and are expected to be photolabile, in a similar manner to fluoroquinolones. Differently to those drugs, oxazolidinones absorb only a part of the UV-B radiation, but in a preliminary attempt we found that when using lamps with emission centered at 360 nm, compound **1** (1×10^{-2} M) decomposes at about half of the rate with similar lamps centered at 310 nm. Thus, one cannot count too much on the poor absorption of near-UV light and drug preparations with compound **1** as the active principle should be protected from light, with attention to the possible phototoxicity,[12,29] even if we are not aware of clinical reports as yet. Furthermore, the arylation of pyrrole suggests that attack at nucleic acids is a possibility. A phototoxic effect[28] may be understood on this basis and on the other hand photoactivated drugs based on this structure may be conceived.

Experimental section

General

H (300 MHz) and C (75.4 MHz) NMR spectra were registered by means of a Brucker instrument and IR spectra by using a Perkin Elmer Fourier transform spectrophotometer. Flash silica gel was used for column chromatographic separation. Reverse phase HPLC spectrometry was carried out by using a C_8 Zorbax SB column and eluting with MeCN–H_2O 3 : 7). The same set up was used for HPLC/MS experiments. Fluorescence and phosphorescence spectra were measured by means of a Perkin Elmer spectrometer. (*S*)-3-[3′-Fluoro-4′-(*N*-morpholino)phenyl]-5-(*N*-acetamidomethyl)-oxazolidin-2-one (linezolid, **1**) was prepared according to the published procedure.[30] The fluorine-free analogue **2**, the pharmacological activity of which has been reported,[31] was prepared in a similar way from 4-(*N*)-morpholinoaniline as indicated below.

(*R*)-3-(4′-*N*-Morpholinophenyl)-5-(hydroxymethyl)-oxazolidin-2-one. To a solution of 4-(*N*)-morpholinoaniline[32] (4.2 g) in water–acetone (50 + 100 mL) at 0 °C, sodium carbonate (4.2 g) was added. After 10 min, benzyl choroformate (3.6 mL) was slowly added and then the mixture was stirred for 4 h at rt. Addition of ice–water gave 7 g (90% yield) of the benzyl urethane, mp. 130–132 °C; elemental analysis C 69.0, H 6.5, N 8.8, $C_{18}H_{20}N_2O_3$ requires C 69.21, H 6.45, N 8.97%; IR (nujol) ν 3290, 1724 cm^{-1}; H NMR ($CDCl_3$) δ 3.2 (t, 4H, $J = 5$ Hz), 3.9 (t, 4H, $J = 5$ Hz), 5.25 (s, 2H), 6.55 (br s, 1H), 6.9 (d, 2H, $J = 9$ Hz), 7.3–7.5 (m, 5H), 7.5 (d, 2H, $J = 9$ Hz); m/z 312 (M^+). A solution of this material in anhydrous THF (110 mL) was brought to −78 °C under nitrogen and treated with butyl lithium (16 mL of a 1.7 M solution in pentane). After 40 min stirring, a solution of (*R*)-glycidyl butyrate

(4.75 mL) in THF (4.75 mL) was added, the mixture stirred for a further hour and then left overnight at rt. Upon adding saturated ammonium chloride (90 mL), ethyl acetate (65 mL) and water (70 mL), two phases formed and were separated. The organic phase was extracted with 3 × 60 mL ethyl acetate. Washing of the reunited extracts with saturated NaCl and evaporation gave the product (2.29 g, 37% yield), mp 156–158 °C; elemental analysis C 60.9, H 6.5, N 9.8, $C_{14}H_{18}N_2O_4$ requires C 60.42, H 6.52, N 10.07%; IR (nujol) ν 3420, 1700 cm^{-1}; H NMR ($CDCl_3$) δ 3.1 (t, 4H, $J = 5$ Hz), 3.75 (m, 1H), 3.9 (t, 4H, $J = 5$ Hz), 3.95–4.05 (m, 3H), 4.75 (m, 1H), 6.9 (d, 2H, $J = 9$ Hz), 7.5 (d, 2H, $J = 9$ Hz); m/z 278 (M^+).

(*R*)-3-(4′-*N*-Morpholinophenyl)-5-(methanesulfonyloxymethyl)-oxazolidin-2-one. The above compound (3.8 g) was dissolved in dry dichloromethane (80 mL) and dry triethylamine (3.75 mL) was added. The solution was brought to 0 °C and methanesulfonyl chloride (1.48 mL) was slowly added while stirring. After further 20 min stirring, the white precipitate was filtered off. Extraction of the aqueous phase with dichloromethane and evaporation gave a solid which was reunited with the original precipitate and recrystallized from acetonitrile–water to yield the product (3.95 g, 80% yield), mp 165–168 °C; elemental analysis C 50.1, H 6.0, N 7.8, $C_{15}H_{20}N_2O_6S$ requires C 50.55, H 5.66, N 7.86%; IR (nujol) ν 1739 cm^{-1}; H NMR [$DCON(CD_3)_2$] δ 3.1 (s, 3H), 3.2 (t, 4H, $J =$ 5 Hz), 3.8 (t, 4H, $J = 5$ Hz), 3.9 (dd, 1H, $J = 6$, 9 Hz), 4.1 (t, 1H, $J = 9$), 4.45 (AA′dq, 2H, $J = 4$, 12 Hz), 4.9 (m, 1H), 6.95 (d, 2H, $J = 9$ Hz), 7.45 (d, 2H, $J = 9$ Hz); m/z 356 (M^+).

(*R*)-3-(4′-*N*-Morpholinophenyl)-5-(azidomethyl)-oxazolidin-2-one. A solution of the above compound (2 g) and sodium azide (1.39 g) in anhydrous THF was heated at 75 °C for 16 h. Upon cooling and treating with water (100 mL) and ethyl acetate (50 mL), two phases formed and were separated. Extraction of the aqueous phase and evaporation of the collected organics gave the product (1.28 g, 74% yield); elemental analysis C 55.9, H 5.3, N 22.8, $C_{14}H_{17}N_5O_3$ requires C 55.44, H 5.65, N 23.09%; IR (nujol) ν 2114, 1730 cm^{-1}; H NMR ($CDCl_3$) δ 3.15 (t, 4H, $J = 5$ Hz), 3.6 (AA′ dq, 2H, $J = 5$, 12 Hz), 3.8 (t, 4H, $J = 4$ Hz), 3.8–3.9 (m, 1H), 4.1 (t, 1H, $J = 9$ Hz), 4.8 (m, 1H), 6.95 (d, 2H, $J = 9$ Hz), 7.5 (m, 2H, $J = 9$ Hz); m/z 303.

(*S*)-3-(4′-*N*-Morpholinophenyl)-5-(*N*-acetamidomethyl)-oxazolidin-2-one (2). The above azide (2.33 g) in ethyl acetate (330 mL) was hydrogenated at room temperature and pressure in the presence of 0.32 g Pd/C. When the reaction was complete (TLC), the mixture was cooled at 0 °C and pyridine (0.65 mL) and acetic anhydride (2.25 mL) were added. After stirring at 0 °C for 30 min, the mixture was brought to rt, filtered and evaporated. The residue was chromatographed on a silica gel column (150 g) eluting with ethyl acetate to give the title compound (1.73 g, 74% yield), colorless solid, mp 174–177 °C, elemental analysis C 60.0, H 6.6, N 13.0, $C_{16}H_{21}N_3O_4$ requires C 60.17, H 6.63, N 13.16%; IR (nujol) ν 3310, 1730 cm^{-1}; H NMR ($CDCl_3$) δ 2.05 (s, 3H), 3.1 (t, 4H, $J = 5$ Hz), 3.5 (ABX, 2H), 3.7–3.85 (m, 2H), 3.9 (t, 4H, $J =$ 5 Hz), 4.05 (t, 1H, $J = 9$ Hz), 4.75 (m, 1H), 6.05 (br t, 1H), 6.95 (d, 2H, $J = 9$ Hz), 7.45 (d, 2H, $J = 9$ Hz); C NMR ($CDCl_3$): δ 22.8 (CH_3), 43.5 (CH_2), 49.3 (CH_2), 51.1 (CH_2), 68.2 (CH_2), 73.7 (CH), 117.6 (CH), 121.8 (CH), 132.4, 150.2, 157.4, 174.3; m/z 319 (M^+).

***N*-(2-Fluorophenyl)-morpholine (10)[33].** The compound was prepared by adapting a method reported for other phenylated morpholines.[34] Bis-(2-chloroethyl)ether (6.5 ml, 0.055 moles) was dissolved in 100 ml butanol and 2-fluoroaniline (5.35 ml, 0.055 moles) was added while stirring at rt and then the mixture was refluxed for 48 h. The solution was cooled to rt, shaken over Na_2CO_3, filtered and refluxed for a further 48 h. The solution was cooled, and water (50 ml) and CH_2Cl_2 (50 ml) were added. Phase separation, extraction of the aqueous phase with 3 × 30 ml CH_2Cl_2 and drying and distillation under vacuum gave 3 ml (0.016 moles, 30% yield) of the title compound as a colorless liquid, elemental analysis C 66.0, H 6.6, N 7.5, $C_{10}H_{12}NOF$ requires C 66.28, H 6.67, N 7.73%; IR (neat) ν 1502, 1120 cm^{-1}; H NMR ($CDCl_3$) δ 3.1 (t, 4H, $J = 5$ Hz), 3.9 (t, 4H, $J = 5$ Hz), 6.8–7.0 (m, 2H), 7.0–7.1 (m, 2H); m/z 181.

Photochemical reactions

General. 6×10^{-3} M Solutions of linezolid were nitrogen flushed and irradiated under either of the two conditions: (a) in an immersion well apparatus (125 mL) by means of a medium pressure mercury arc or (b) in a number of quartz tubes (each 10 mL) by means of 4 external phosphor coated lamps (centre of emission, 310 nm). The course of the reaction was monitored by HPLC. When the starting material was consumed, the solvent was removed by rotary evaporation and the crude product was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate). The key data for the identification of the isolated new photoproducts are reported below. Compound **2** has been characterized above and compound **3** was recognized on the basis of the spectroscopic properties identical to those previously reported.[12] For the other products, HPLC/MS data were used for structure proposals: compounds **4**, m/z 338 (M^+, 100); **5**, m/z 338 (M^+, 100); **6**, m/z 318 (M + H^+, 100%) (for compounds **4–6** compare ref. 12; **9**, m/z 338 (M^+, 100). The main characteristics of the other photoproducts are reported below. *N*-(2-Fluorophenyl)morpholine (**10**) was irradiated in the same way (option b above) to form the hydroxy derivative **11** (see below) and reduced **12** (identical to a commercial sample).

3′-d (*S*)-3-(4′-*N*-Morpholinophenyl)-5-(*N*-acetamidomethyl)-oxazolidin-2-one (d-2). This differed from the non-deuterated analogue **2** (see above)[12] for the following features: H NMR ($CDCl_3$) δ 6.95 (1H rather than 2H); C NMR ($CDCl_3$) δ 117 (CD); m/z (%) 320 (M^+, 100).

(*S*)-3-[3′-Methoxy-4′-(*N*-morpholino)phenyl]-5-(*N*-acetamidomethyl)-oxazolidin-2-one (7). Oil that solidifies on standing; IR (nujol) ν 1743 cm^{-1}; elemental analysis C 58.8, H 6.7, N 11.9, $C_{17}H_{23}N_3O_5$ requires C 58.44, H 6.64, N 12.03%; H NMR ($CDCl_3$) δ 2.1 (s, 3H), 3.05 (t, 4H $J = 5$ Hz), 3.7–3.85 (m, 3H), 3.85 (t, 4H $J = 5$ Hz), 3.85 (s, 3H), 4.1 (t, 1H $J = 9$ Hz), 4.7 (m, 1H), 6.15 (br t, 1H), 6.75 (dd, 2H $J = 2$, 9 Hz), 6.9 (d, 1H $J = 9$ Hz), 7.4 (d, 1H $J = 2$ Hz). C NMR ($CDCl_3$) δ 23.0 (CH_3), 41.9 (CH_2), 47.8 (CH_2), 51.1 (2 CH_2), 55.5 (CH_3), 67.0 (2 CH_2), 71.7 (CH), 103.0 (CH), 110.1 (CH), 117.8 (CH), 132.4, 150.2, 157.5, 174.3.

(*S*)-3-[3′-Iodo-4′-(*N*-morpholino)phenyl]-5-(*N*-acetamidomethyl)-oxazolidin-2-one (8). Colorless solid, mp 200–203 °C; IR (nujol) ν 1737 cm^{-1}; elemental analysis C 42.9, H 4.5, N 9.3, $C_{16}H_{20}N_3O_4I$ requires C 43.16, H 4.53, N 9.44%; H NMR

[$(CD_3)_2SO$] δ 1.85 (s, 3H), 2.9 (t, 4 H, $J = 5$ Hz,), 3.3 (ABX, 2H), 3.7 (m, 1H), 3.75 (t, 4H, $J = 5$ Hz), 4.1 (t, 1H, $J = 9$ Hz), 4.7 (m, 1H), 7.2 (d, 1H, $J = 9$ Hz), 7.5 (dd, 1H, $J = 2.5$, 9 Hz), 8.1 (d, 1H, $J = 2.5$ Hz), 8.2 (t, 1H, $J = 6$ Hz); C NMR [$(CD_3)_2SO$] δ 22.8 (CH_3), 40.4 (CH_2),47.7 (CH_2), 52.9 (2 CH_2), 66.8 (2 CH_2), 71.9 (CH), 98.6 (CI), 119.5 (CH), 121.4 (CH), 129.3 (CH), 133.4, 137.8, 152.5, 154.4, 171.0.

(*S*)-3-[3′-(2-Pyrrolyl)-4′-(*N*-morpholino)phenyl]-5-(*N*-acetamidomethyl)-oxazolidin-2-one (10). Colorless solid, mp 56–58 °C; elemental analysis C 62.4, H 6.3, N 14.9, $C_{20}H_{24}N_4O_4$ requires C 62.49, H 6.29, N 14.57%; IR (nujol) ν 1740 cm^{-1}; H NMR (CD_3OH) δ 1.9 (s, 3H), 2.8 (t, 4H, $J = 5$ Hz,), 3.5 (ABX, 2H), 3.8 (m, 1H), 3.8 (t, 4H, $J = 5$ Hz), 4.1 (t, 1H, $J = 9$ Hz), 4.7 (m, 1H), 6.2 (t, 1H, $J = 2$ Hz), 6.5 (dd, 1H, $J = 2$, 3.5 Hz), 6.9 (dd, 1H, $J = 2$, 3.5 Hz), 7.1 (d, 1H, $J = 9$ Hz), 7.3 (dd, 1H, $J = 3$, 9 Hz), 7.6 (d, 1H, $J = 3$ Hz); C NMR (CD_3OH) δ 22.8 (CH_3), 43.5 (CH_2), 49.8 (CH_2), 53.8 (2 CH_2), 68.4 (2 CH_2), 73.7 (CH), 108.5 (CH), 109.8 (CH), 118.0 (CH), 118.8 (CH), 120.1 (CH), 121.1 (CH), 129.4, 131.3, 135.8, 146.7, 157.2, 174.0.

***N*-(2-Hydroxyphenyl)-morpholine (11).**[35] Colorless solid, mp 130 °C; elemental analysis C 66.5, H 7.4, N 7.4, $C_{10}H_{13}NO_2$ requires C 67.02, H 7.31, N 7.82%; IR (nujol) ν *ca.* 3000 (br), 1454 cm^{-1}; H NMR ($CDCl_3$) δ 3.0 (t, 4H, $J = 5$ Hz), 3.95 (t, 4H, $J = 5$ Hz), 6.9 (dt, 1H, $J = 7.5$, 1.5), 7.0 (dd, 1H, $J = 1.5$, 7.5), 7.1 (dt, 1H, $J = 1$, 7.5), 7.2 (dd, 1H, $J = 1$, 7.5); C NMR ($CDCl_3$) δ 52.7 (2 CH_2), 66.5 (2 CH_2), 114.2 (CH), 120.1 (CH), 121.3 (CH), 126.6 (CH), 138.6, 151.4.

Quantum yield measurements

Reaction quantum yields were measured by irradiating 2 mL samples of 5×10^{-4} M solutions of either **1** or **2** in a quartz spectrophotometric cuvette on an optical bench. The light source was a collimated beam from a 100 W high-pressure mercury arc fitted with an interference filter (transmittance maximum, 280 nm). The reaction was monitored by HPLC and the consumption of the starting material (limited to <20%) was determined (a known volume—20 µl—injection loop was used). The light flux was measured by ferrioxalate actinometry. Fluorescence quantum yields were measured by using quinine sulfate as the standard ($\Phi_F = 0.54$).

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