Fully selective intramolecular *ortho* photocycloaddition of 4-(4-methoxyphenoxy)-3-(*N*³-benzoylthymin-1-yl)but-1-ene: an unprecedented benzene–thymine photocycloaddition

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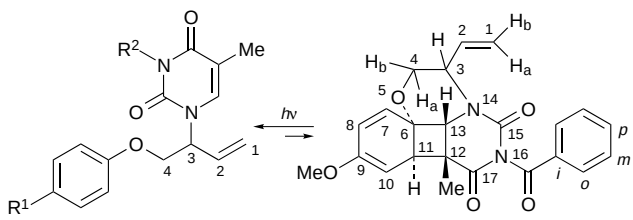
On irradiation of 4-(4-methoxyphenoxy)-3-(*N*³-benzoylthymin-1-yl)but-1-ene 1 at 254 nm in THF a single photoadduct 2 is formed as a result of chemo-, regio- and stereo-selective intramolecular *ortho* photocycloaddition of the thymine double bond to the 1,2-positions of the phenyl ring.

Covalent modification of DNA may occur by photochemical activation of complexes between intercalating drugs and DNA, and between proteins and DNA. 4-(4-Methoxyphenoxy)-3-(*N*³-benzoylthymin-1-yl)but-1-ene **1** can be considered as a model structure to study this cross-linking reaction. Compound **1** represents an arene–alkene bichromophore separated by a tether of three atoms. Intra- as well as inter-molecular photocycloadditions in such compounds are well documented.[1] Both *ortho* and *meta* photocycloadditions of the alkene to the arene have been observed, while the preferred reaction mode depends on subtle stereoelectronic effects. It was shown that the presence of a methoxy group in an *ortho* position favours attack of the alkene at the 1,2-positions.[2] On the other hand, 4-phenoxybut-1-enes undergo mainly 2,6-*meta* photocycloaddition.[2] Furthermore, introduction of a group allylic to the alkene has a major influence on the reaction outcome.[3] We were interested in examining the photocycloaddition of 4-(4-methoxyphenoxy)-3-(*N*³-benzoylthymin-1-yl)but-1-ene **1**, in which these features are combined. Moreover, this compound allowed us to study the competition between the alkene and the 5,6-double bond of the thymine ring in the photocycloaddition reaction. Additionally, we investigated the photoreactivity of compounds **3**–**5** as analogues of **1**.

Trichromophore **1**‡ was synthesized by reaction of 4-methoxyphenol with butadiene monoxide in Me_2SO in the presence of KOH,§ followed by coupling of the resulting 3-hydroxy-4-(4-methoxyphenoxy)but-1-ene (57%) with *N*³-benzoylthymine under Mitsunobu conditions (40%).[4] Irradiation of **1** in THF (50 mg in 20 ml, 254 nm, 20 min) yielded a single photoproduct **2** (23%) in addition to unchanged starting material. Increasing the reaction time (up to 90 min) did not appreciably change the ratio of **1** to **2** before formation of degradation products started. Photoadduct **2** was isolated by preparative HPLC on silica using ethyl acetate–hexane (3:7) as eluent. Irradiation (1 h) of **2** under conditions identical to those used for **1** afforded a mixture of **1** and **2** in approximately the same ratio as observed for the forward reaction.



1 R^1 = OMe; R^2 = Bz
3 R^1 = H; R^2 = Bz
4 R^1 = OMe, R^2 = H
5 R^1 = H; R^2 = H

2

The structure of **2**‡ (arbitrary numbering) was fully elucidated by ^{1}H and ^{13}C NMR. Analysis of the ^{13}C NMR data clearly revealed eight instead of four signals for aliphatic carbons, in addition to the five benzoyl peaks and eight other sp²-carbon signals. From a DEPT spectrum the presence of an intact vinyl group was inferred (a methylene sp²-carbon at δ 118.71 and a methine sp²-carbon at δ 131.64), together with two carbonyls (δ 169.38 and 150.51), an oxygenated non-protonated carbon (δ 155.48) and three methine sp²-carbons at δ 129.35, 124.90 and 87.81. The two typical C-5 and C-6 thymine sp²-resonances were absent. Apparently, chemoselective *ortho*-photocycloaddition of the thymine double bond at the 1,2-positions of the phenyl group had taken place leaving the vinyl group unaltered. Although [2 + 2] photocycloadducts of thymine and its derivatives are well known,[5] the type of arene–alkene photocycloaddition observed in this study is to our knowledge unprecedented.

The structure‡ of this photocycloadduct was further confirmed by a complete analysis of the ^{1}H NMR spectrum *via* COSY and HETCOR experiments. The stereochemical relationships were derived from NOE experiments. The *cis* configuration of the methyl group and the methine proton (H-13), originally being H-6 of thymine, was established, as well as the *trans* relationship between the methyl group and the methine proton (H-11) originally at the *ortho* position of the alkoxy chain. Obviously, the rings annelated to the cyclobutane moiety are in the *cis–anti–cis* configuration. The [2 + 2] photocycloaddition is indeed expected to occur in the *cis* mode,[6] while the steric requirements are accomodated by the less constrained *anti* configuration. The stereochemistry at the remaining chiral centre (C-3) can be deduced on account of the conformational features of the 1-aza-4-oxacyclohexane ring. The proton is in a pseudo-axial position (*S*-configuration in structure **2**) as ascertained by the magnitude of the coupling constants with the vicinal H-4 protons (9.4 and 8.0 Hz) and by the observation of a NOE enhancement between H-3 and H-4b and not with H-4a. The existence of a NOE between the *ortho* hydrogen of the benzoyl group and H-11, and between the methyl group and H-8 and H-10, supports the stereochemical assignment.

The exclusive formation of photocycloadduct **2** can be rationalized in terms of the control elements present in **1**. The *ortho* photocycloaddition is accounted for by the presence of the *para*-methoxy group, which should exhibit similar electronic behaviour to an *ortho*-methoxy group.[2] A similar preference for the *ortho* reaction was also noted for 3-acetoxy-4-(4-methylphenoxy)but-1-ene.[7] On the other hand, the more pronounced polarization of the thymine double bond in comparison with the vinyl group would preferably lead to *ortho* addition, as this reaction mode predominates when the ionization potentials of the reacting entities differ to a certain extent.[8] Dimerization

usually encountered in thymine derivatives is prevented by carrying out the reaction in dilute medium and also by the efficiency of the intramolecular photocycloaddition.

Interestingly, independent irradiation of N^3-benzoylthymine and 4-phenoxy-3-(N^3-benzoylthymin-1-yl)but-1-ene **3**, under the same conditions as described, resulted in complete substrate consumption yielding mainly polar constituents, in which loss of the benzoyl group was evident from the NMR data. Analogous thymine-unprotected compounds, such as 4-(4-methoxyphenoxy)-3-(thymin-1-yl)but-1-ene **4** and 4-phenoxy-3-(thymin-1-yl)but-1-ene **5**, proved to be light-stable, even after prolonged irradiation (24 h). It is, therefore, deduced that the presence of both the *para*-methoxy and the N^3-benzoyl groups is required in order to direct the intramolecular arene–alkene photocycloaddition thereby showing the sensitivity of this reaction to subtle and unexpected substituent effects. The *para*-methoxy group apparently creates suitable electronic conditions for *ortho* addition, while it remains to be clarified whether the benzoyl group activates or the secondary amide inhibits photocycloaddition.

In most instances, the *ortho* adducts, resulting from intramolecular arene–alkene photocycloaddition, suffer from further reactions depending on the varying stabilities of the particular compounds formed in the cascade. The bicyclo[4.2.0]octa-2,4-diene unit, present in such *ortho* photoadducts, normally rearranges on heating into a cyclooctatriene, which subsequently gives a mixture of [2 + 2] photocycloadducts. Only occasionally have primary *ortho* photoadducts been isolated as stable compounds, as was found on irradiation of pentafluorophenylprop-2-enyl ether,[9] 2-methyl-6-(4-fluorophenyl)-hex-2-ene[10] and 1-(2-methoxybenzyloxy)-3-methylbut-2-ene.[11] In the present case, after heating **2** in refluxing THF for several hours we were not able to detect cyclooctatriene-like structures, nor was there any evidence for a Diels–Alder-type reaction between the alkene and the cyclohexa-1,3-diene units present in **2**.

In conclusion, we have observed the intriguing photoreactivity of trichromophore **1** since a single, stable *ortho* photoadduct **2** arose under full chemo-, regio- and stereo-selective control. This unprecedented reaction may imply potential cross coupling of pyrimidine bases in nucleic acids with aromatic amino acids in proteins or with intercalating drugs by virtue of a [2 + 2] photocycloaddition, thereby inducing DNA alterations which may interfere with biological function. Hitherto, it was known that amino acids could photochemically add across the double bond of pyrimidine bases,[12] but results obtained for the present model system may shed light on yet different photochemical nucleic acids–protein and/or nucleic acids–drug interactions.

Financial support by the Special Research Fund of the University of Gent (project number 01109394) to D. D. K is gratefully acknowledged.

Footnotes

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‡ Satisfactory spectral data for compounds **1** and **2** were obtained that were consistent with the assigned structures and satisfactory elemental analyses or high-resolution mass spectra were obtained. Data for **1**: mp 121.5–122 °C. R_f (hexane–ethyl acetate, 7 : 3): 0.24. ν (KBr)/cm^{-1} 1753, 1702, 1656, 1509, 1231. λ_{max}/nm (MeOH) (ε): 206 (26 500), 226 (16 000), 254 (18 600), 274 (11 100). δ_H (360 MHz, $CDCl_3$) 1.96 (3 H, s, T-Me) 3.78 (3 H, s, OMe), 4.24 (1 H, dd, 10.3 and 4.1 Hz, H-4a), 4.30 (1 H, dd, 10.3 and 5.6 Hz, H- 4b), 5.42 (1 H, m, H-3), 5.47 (1 H, dd app. d, 17.4 Hz, H-1a), 5.52 (1 H, dd app. d, 10.8 Hz, H-1b), 6.07 (1 H, ddd, 17.3, 10.7 and 5.7 Hz, H-2), 6.85 (4 H, s, Ar), 7.35 (1 H, s, T-6), 7.47 (2 H, t, 7.8 Hz, Bz), 7.64 (1 H, t, 7.4 Hz, Bz), 7.90 (2 H, dd app. d, 7.8 Hz, Bz). δ_C (360 MHz, $CDCl_3$): 12.46 (T-Me), 55.62 (OMe), 55.83 (C-3), 68.48 (C-4), 110.34 (T-5), 114.74 (Ar-*o*), 115.70 (Ar-*m*), 120.89 (C-1), 128.98 (Bz-*m*), 130.31 (Bz-*o*), 131.56 (C-2), 131.63 (Bz-*i*), 134.78 (Bz-*p*), 138.19 (T-6), 149.96, 152.00 (Ar-*i* and -*p*), 154.51 (T-2), 162.60 (T-4), 168.80 (Bz-CO). MS: 407 ($M^{+\cdot}$ + H^+; 10), 105 (100). For **2**: mp 173.7 °C. R_f (pentane–ethyl acetate, 6 : 4): 0.53. ν (KBr)/cm^{-1} 1743, 1700, 1673, 1437, 1232, 897, 796, 730. λ_{max}/nm (MeOH) (ε): 206 (21 500), 250 (16 800), 284 (3900). δ_H (Gemini 200 MHz, $CDCl_3$) 1.39 (3 H, s, Me^{12}), 3.53 (1 H, dd, −12.3 and 9.4 Hz, H-4a), 3.60 (3 H, s, OMe), 3.65 (1 H, d, 1.2 Hz, H-13), 4.01 (1 H, br d, *J* 6.9 Hz, H-11), 4.03 (1 H, dd, −12.2 and 8.0 Hz, H-4b), 4.58 (1 H, br d, 6.8 Hz, H-10), 5.03 [1 H, qt, 8 Hz (3 ×), H-3], 5.32 (1 H, dt, 10.3 and −1.3 Hz, H-1a), 5.34 (1 H, dt, 17.3 and −1.3 Hz, H-1b), 5.75 (1 H, ddd, 17.3, 10.3 and 5.6 Hz, H-2), 6.07 (1 H, dt, 10.3 and 1.3 Hz, H-7); 6.15 (1 H, dd, 10.1 and 1.9 Hz, H-8), 7.50 (2 H, tm, 7.4 Hz, Bz-*o*), 7.64 (1 H, tt, 7.3 and 1.4 Hz, Bz-*p*), 7.94 (2 H, dm, 7.1 Hz, Bz-*m*). δ_C (Gemini 200 MHz, $CDCl_3$) 16.84 (Me^{12}), 40.24 (C-12), 47.72 (C-11), 51.58 (C-3), 54.84 (OMe), 56.56 (C-13), 62.41 (C-4), 70.00 (C-6), 87.81 (C-10), 118.71 (C-1), 124.90 (C-7), 129.04 (Bz-*m*), 129.35 (C-8), 130.12 (Bz-*o*), 131.64 (C-2), 132.59 (Bz-*i*), 134.62 (Bz-*p*), 150.51 (C-15), 155.48 (C-9), 169.38 (C-17), 170.57 (Bz-CO). MS: 407 ($M^{+\cdot}$ + H^+; 5); 105 (100).

§ Cleavage of epoxides usually requires attack by reactive nucleophiles as described by Posner and Rogers (*J. Am. Chem. Soc.*, 1977, **99**, 8208). We were able to effect the reaction using 4-methoxyphenolate in Me_2SO (57%). In the absence of the activating *para*-methoxy group the yield is significantly decreased (20%).

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Received, 23rd January 1997; Com. 7/00554G