BORON TRIFLUORIDE CATALYSIS OF
PHOTODIMERIZATION OF COUMARINS AND PSORALENS
AND THEIR CROSS CYCLOADDITION TO
TETRAMETHYLETHYLENE

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Résumé : Nous étudions les effets de la complexation par BF3 sur les réactions de photodimérisation et de photo cycloaddition, avec le 2,3-diméthyl-2-éne, de la coumarine 1, des 5-méthoxy et 5,7-diméthoxycoumarines 2 et 3 et des 5- et 8-
méthoxypsoralènes 4 et 5. L’observation de points isobasiques dans les spectres électroniques et de modifications des spectres IR en présence de BF3, indiquent la formation d’un complexe entre l’acide de Lewis et l’oxygène du groupement carbonyl du cycle pyrène. La formation d’un exciplex singulet conduit à une augmentation du rendement et de la stéréodirection de la réaction. BF3 se comporte comme un catalyseur pour les réactions impliquant le passage par un état singulet et comme un inhibiteur pour celles impliquant un état triplet.

Mots clés : Coumarines, Psoralènes, Photodimérisation, Photo cycloaddition, Acide de Lewis.

1 - INTRODUCTION

The photo reaction of coumarine and psoralenes has been extensively investigated, notably the dimerisation and cycloaddition using alkenes, DNA and its pyrimidine bases. The furcoumarines compounds are

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able to intercalate inside DNA, and by subsequent irradiation with UVA light, to photoreact with DNA. The photoreaction already known, consists of a (2+2) cycloaddition reaction with the pyrimidine bases [11]. However, results are often scanty and rarely comparable because of differences in experimental conditions. Nevertheless, it is well known that photochemical processes are complex, and parameters such as: concentration, temperature, physical status, type of solvent, etc. can significantly influence photochemical reaction processes.

Furthermore, the 7-methoxycoumarin 2 and the 5, 7-dimethoxy-
coumarin 3 (scheme 1) were extensively studied under various conditions. The study of these two compounds were systematically reconsidered mainly with regard to dimerisation and photocycloaddition processes with tetramethylethylene (TME) under similar experimental conditions, in order to monitor their photochemical behaviour.

In the past, only the substituted furcocumarin, 8-methoxypsoralen 5 was the compound used in phototherapy of a number of skin diseases such as psoriasis and vitiligo [12]. Numerous studies were conducted on the photochemical behaviour of this compound under different experimental conditions in order to get a better understanding of its photo biological and photo medical properties. However in the past two decades, the negative mutagenic effect of this compound responsible for skin cancer was observed. For this reason, physicians and biologists are now trying to turn to other more efficient and less toxic compounds. The 5-methoxypsoralen, compound 4 has been used for the past decade as an efficient drug in the treatment of psoriasis. This drug tends to replace 8-
methoxypsoralen 5. Despite genotoxic properties, it causes less adverse effects and is well tolerated by patients.

This compound has received little attention and as a result, its photochemical properties are not well known. This led us to consider that a study of these two compounds in similar experimental conditions is a necessity.
Photoactivity studies of the two furano-quinodimethanes *vis-a-vis* the dimerisation and the addition processes of an alkene (TME) were undertaken under conditions similar to those used previously. The aim was to compare the two molecules and to try to show the influence of the furan nucleus on the coumarins.

Photosensitisation and quenching play a significant role in photochemistry. The ability of Lewis acids to serve as a catalyst for photochemical reactions has been recognized for many years [4]. In particular Lewis acids serve as catalysts for photochemical (2+2) cycloaddition reaction such as photodimerization [5-9]. Shim [10] has also studied the influence of Lewis acids on the photoactivity of 5,7-dimethoxycoumarin. We found it necessary to repeat previous experiments in the presence of BF$_3$OEt$_2$ in order to analyse the effects of BF$_3$ on reactional processes. So, we investigated spectroscopic properties, photodimerisation and cross photocyclodensation with tetramethylethylene (TME) of coumarin 1, the two methoxycoumarins, 2, 3 and methoxyphtalens 4, 5 (Scheme 1), in the presence and the absence of boron trifluoride etherate as Lewis Acid.

\begin{align*}
1: & R_1 = R_2 = H \\
2: & R_1 = H; R_2 = \text{OCH}_3 \\
3: & R_1 = R_2 = \text{OCH}_3 \\
4: & R_1 = \text{OCH}_3; R_2 = H \\
5: & R_1 = H; R_2 = \text{OCH}_3
\end{align*}
EXPERIMENTAL

Materials
Coumarins, psoralens, 2,3-dimethyl but-2-ene and boron trifluoride etherate were purchased from Aldrich and used as received except for 5,7-dimethoxycoumarin which was sublimated before use. Dichloromethane was treated with a 5% solution of sodium carbonate, dried over calcium chloride and distilled before use. Other solvents (pure grade) were used without further purification.

General Methods
Ultraviolet absorption spectra were obtained on a Beckman Model 25 spectrometer. Solid state infrared spectra were recorded on a 7199 Nicolet FT-IR spectrometer with 2 cm⁻¹ resolution using KBr pellets. ¹H NMR spectra were measured in CDCl₃ or in DMSO-D₆ using a Varian EM 360 (60 MHz) or a Bruker 200 Spectrometer (200 MHz), or a Bruker AM 400 Spectrometer (400 MHz). The chemical shifts, are relative to tetramethylsilane and expressed in parts per million (ppm), the coupling constants are in hertz.

Irradiation Procedures
The samples were irradiated 45 cm from the light source, with 450 W high pressure mercury lamp (230 < λ < 900 nm) equipped with a quartz envelope. The glass reaction cells filtered the beam at λ > 310 nm. Reactions were monitored by UV-visible spectrometry. After irradiation the samples were concentrated by rotary evaporation under reduced pressure. The crude photoproducts were analysed by ¹H NMR and IR before purification. Photoproducts were isolated by fractional crystallization and the purities controlled by ¹H NMR spectroscopy at 400 MHz.

Irradiation in Presence of BF₃·OEt₂ - General Procedure
Compounds were dissolved in 50 ml of dichloromethane in a pyrex
flask and the degassed solution with \( \text{N}_2 \), \( \text{BF}_3\text{OEt}_2 \) was added to the sample with a syringe and the flask scales under vacuum. The sample was then irradiated for many hours, table 1.
Table 1: Product composition for dimerization experiments. a: This work; b: see ref. 14; c: see ref. 4d; d: sensitized photolysis ref 1b; e: see ref. 3a; f: see ref. 8d, and 9; the same result is obtained in sensitized experiment; g: see ref. 16.
Irradiation with TME in Presence of BF₃OEt₂ General Procedure

Compounds and BF₃OEt₂ were combined with dichloromethane in the pyrex cell and allowed to stand for approximately 15 minutes. Tertamethyl ethylene (1.18 ml, 10⁻² mol) was then added to the flask and the solution diluted to 50 ml with additional dichloromethane. The cell was degassed, sealed and irradiated with 450 W lamp for 4h, Table II.
Table II: Yield of Cross photocycloaddition reactions. a: This work, In any experiments we have a large excess of TME. Irradiation time is 4 hours. b: see ref. 14; c: see ref. 41; d: we obtain also 5% of cis- and photodimer; e: see ref. 46; f: see ref. 6d.

<table>
<thead>
<tr>
<th>Unsaturated Epoxides</th>
<th>Catalyst Experiments</th>
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<tbody>
<tr>
<td></td>
<td>BF$_3$OEt$_2$</td>
</tr>
<tr>
<td>Compound</td>
<td>Concentration M$^{-1}$</td>
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<tr>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>2$^a$</td>
<td>0.02</td>
</tr>
<tr>
<td>2$^b$</td>
<td>0.02</td>
</tr>
<tr>
<td>2$^c$</td>
<td>0.02</td>
</tr>
<tr>
<td>3$^e$</td>
<td>0.005</td>
</tr>
<tr>
<td>3$^f$</td>
<td>0.02</td>
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<tr>
<td>3$^g$</td>
<td></td>
</tr>
<tr>
<td>4$^h$</td>
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<tr>
<td>5$^i$</td>
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</tr>
<tr>
<td>5$^j$</td>
<td>0.02</td>
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<tr>
<td>5$^k$</td>
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</table>

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RESULTS AND DISCUSSION

Table I shows experimental results for uncatalyzed and boron trifluoride catalyzed dimerization. In Table II experimental results for uncatalyzed and catalyzed photocycloaddition with TME are reported. Our results are compared with those previously obtained by Lewis and Shim for 1,5,7-dimethoxycoumarin 3 and 8-methoxypsoralen 4. To eliminate the influence of solvent on the product ratio and to provide a basis for comparison of Lewis acid catalyzed versus uncatalyzed reactions, we have carried out the experiments in dichloromethane solutions. The different photocyclization products in the crude solid obtained after evaporation of the solvent of the irradiated samples, were purified by fractional crystallization. Their purities were controlled by $^1$H NMR spectroscopy at 400 MHz.

In our experiments with 5- and 8-methoxypsoralens the (2+2) cycloaddition occurs exclusively at the C$_3$-C$_4$ double bond of the pyrone ring, as observed previously. In contrast, the photoreaction of psoralen derivatives and other analogue compounds with the thymidine bases of DNA, proceeds with cross-linking in both the double bond sites of the furan C$_4$-C$_5$ and the pyrone C$_3$-C$_4$ rings. The furan double bond is the more reactive, but this fact is some times debated.

The structures of the photodimers (Scheme 2) were established by comparison of their $^1$H NMR and IR spectra with those described in the literature for similar products (Table III). Four photodimers can be expected with a cis-syn, cis-anti, trans-syn or trans-anti organization around the cyclobutane ring resulting from the (2+2) cycloaddition (Scheme 2).
Scheme 2

- clc-syn
- clc-anti
- trans-syn

R₁ = R₅ = H; coumarin
R₂ = R₄ = COOH; 7-methoxycoumarin
R₃ = R₆ = COOH; 5,7-dimethoxycoumarin

R₁ = COCH₃; R₅ = H; 5-methoxybenzaldehyde
R₂ = R₄ = COOH; 3-methoxyphenylacetate

Scheme 2
Table III: Infrared spectra of monomers and dimers. VS: very strong. (The underlined vibrations are the strongest)
Uncatalyzed Reactions

From the results summarized in Tables I and II, we can observe that for the uncatalyzed reactions the yield is enhanced by a methoxy substituent, as previously observed [6b]. Likewise a methoxy group in position 5 of pyranones is more efficient than in position 8. As generally observed, Lewis [4d] showed that for coumarins 1, cis-syn and cis-anti cycloadduct compounds proceed from singlet excited state and trans-syn and trans-anti cycloadducts from triplet state. From fluorescence and phosphorescence experiments, Mantulin and Song [14] concluded to singlet excited state for 2 and 3 and triplet ones for hydroxy pyranones derivatives.

Now if we analyze the configurations of the dimers in Table 1, we can observe that their structures are correlated with the nature of the excited state, for example, the cis-syn and cis-anti dimers are the major photoproducts for coumarins 2 and 3. From these results we can conclude that uncatalyzed dimerization proceed from singlet and triplet states for 1, 2, 3 and exclusively from triplet states for 4 and 5.

For uncatalyzed reaction of compounds 1, 2, 3, 4 and 5 with TME we obtain only cycloaddition on the pyrone ring (scheme 3, table IV). Our results are in agreement with those of Brehe and al [10] who have studied the photocycloaddition of furanocoumarins derivatives with TME, and obtained a cyclobutane monoaadduct with this olefin at the pyrone C1-C4 double bond side. This data also fully correlate with those of the cycloadducts of coumarins to the same alkene [14] and to thymine [10].
Scheme 2: Structures of the photoproduct of the TME

1a: R₁ = R₂ = H
2a: R₁ = H; R₂ = OCH₃
3a: R₁ = R₂ = OCH₃
4a: R₁ = OCH₃; R₂ = H
5a: R₁ = H; R₂ = OCH₃
Table IV: Spectroscopic data of photoadducts with TME.

<table>
<thead>
<tr>
<th></th>
<th>ν C = 0(^\circ)</th>
<th>(^1)H NMR(^\circ)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1745</td>
<td>0.75 (3H, d, 1.02 (3H, s), 1.22 (3H, s), 1.27 (3H, s), 3.18 (1H, d, J=10), 3.38 (1H, d, J=10), 7.10 (4H, m))</td>
</tr>
<tr>
<td>2</td>
<td>1735</td>
<td>0.72 (3H, s), 1.02 (3H, d, J=10), 1.20 (3H, s), 1.27 (3H, s), 3.13 (1H, d, J=10), 3.35 (1H, d, J=10), 5.57 (1H, d, J=2), 6.65 (1H, d, J=2), 6.70 (1H, d, J=2)</td>
</tr>
<tr>
<td>3</td>
<td>1755</td>
<td>0.72 (3H, s), 1.03 (3H, s), 1.18 (3H, s), 1.28 (3H, s), 3.07 (1H, d, J=10), 3.47 (1H, d, J=10), 3.82 (6H, s), 5.17 (2H, s)</td>
</tr>
<tr>
<td>4</td>
<td>1750</td>
<td>0.72 (3H, s), 1.03 (3H, s), 1.22 (3H, s), 1.31 (3H, s), 3.12 (1H, d, J=10), 3.72 (1H, s), 4.2 (3H, s), 6.77 (1H, d, J=2), 7.7 (1H, d, J=2)</td>
</tr>
<tr>
<td>5</td>
<td>1744</td>
<td>0.73 (3H, s), 1.03 (3H, s), 1.20 (3H, s), 1.30 (3H, s), 3.13 (1H, d, J=10), 3.51 (1H, d, J=10), 4.18 (3H, s), 6.63 (1H, d, J=2), 8.8 (1H, s), 7.53 (1H, d, J=2)</td>
</tr>
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</table>
Catalyzed Reactions

Before any comparison between the uncatalyzed and catalyzed reactions, it was necessary to know for each compound the effects of BF₃OEt₂ on the photodimerization and on the photocycloaddition.

Complexation by BF₃OEt₂

The shift of the \( \nu \text{C=O} \) stretching vibration to lower frequency observed by infrared spectroscopy shows that the addition of Lewis acid to the compound in solution causes complexation on the carbonyl oxygen.\(^{14,15}\) This fact is controlled by the evolution of the initial UV spectra of the compounds. For example addition of a small amount of BF₃OEt₂ to a solution of 4 leads to a reduction of the 308 nm absorption band and the appearance of a shoulder at \( \lambda \approx 334 \) nm. For this compound, we observe (Figure 1a), an isobestic point at \( \lambda = 322.5 \) nm indicative of this complexation. A similar result was obtained for 7-methoxy coumarin 2: diminution of the 320 nm absorption band, apparition of a new absorption at \( \lambda = 350 \) nm with existence of an isobestic point at \( \lambda = 333 \) nm (Figure 1b).
Figure 1a: Absorption of $4.2 \times 10^{-5}$ mol. l$^{-1}$ solution of 4 in the absence of BF$_2$OEt$_2$ (a), in the presence of 1.5 $\times 10^{-5}$ mol. l$^{-1}$ (b), 2.4 $\times 10^{-5}$ mol. l$^{-1}$ (c) and 6.5 $\times 10^{-5}$ mol. l$^{-1}$ (d) of BF$_2$OEt$_2$. The isobestic point is observed at $\lambda = 322.5$ nm.

Figure 1b: Absorption of $9.05 \times 10^{-6}$ mol. l$^{-1}$ solution of 2 in the absence of BF$_2$OEt$_2$ (1). In the presence of 4.54 $\times 10^{-5}$ mol. l$^{-1}$ (2), 7.95 $\times 10^{-5}$ mol. l$^{-1}$ (3) and 9.08 $\times 10^{-5}$ mol. l$^{-1}$ (4) of BF$_2$OEt$_2$. The isobestic point is observed at $\lambda = 333$ nm.
Effects on the Photoreactivity

In Figures II and III respectively are summarized the evolution of the yields for the dimerization and for the cross photocycloaddition of 2 and 5 with different concentrations of BF$_3$OEt$_2$. As observed for coumarin [51] in the case of 2 (Figure IIa) the dimerization first increased and then decreased with BF$_3$OEt$_2$ concentration higher than 0.25 equivalent. Similar results were obtained for the cycloaddition reaction with TME (Figure IIb) but the maximum yield is obtained with higher concentrations (0.5 equivalent). In contrast for 8-methoxypsoralen 5, the yield of the two reactions decreases rapidly, as shown in figures IIIa and IIIb. In the case of 4 no dimer formation was observed in the presence of 0.25 equivalent of BF$_3$OEt$_2$ (Table I). This evolution is similar to those reported by Shim in the case of 3[5a].

To compare catalyzed versus uncatalyzed reactions, each catalyzed experiment was carried out with the optimized BF$_3$OEt$_2$ concentrations as is reported in Tables I and II. Results of catalyzed reactions (Tables I and II) show a characteristic enhancement of the stereospecificity (only one photodimer observed) if we exclude compound 3[5] we observe two different behaviours for the photochemical reactivity. For compounds 1 and 2, the enhanced photochemical reactivity of noncomplexed reactions may be interpreted as an increased singlet lifetime state. Therefore, for compounds 4 and 5, which involve triplet reaction pathway, through intersystem crossing, the decreasing photochemical reactivity in catalyzed reactions is easily expected by quenching of the singlet state. For compounds 3 and 5, a plot of R/R$_0$ versus BF$_3$OEt$_2$, where R$_0$ and R are the reaction yield without and with quencher respectively, gives a straight line as predicted by Stern-Volmer quenching equations. The values of the slopes (117 and 262 mol$^{-1}$) show that BF$_3$OEt$_2$ is a better quencher for psoralens than coumarins.
Figure II: Yields for dimerization (a) and cross cycloaddition with TME (b) of 2 (2.10^5 M) in the presence of BF3 OEt2.
Figure 11: Yields for dimerization (a) and cross cycloaddition with TME (b) of 
5 (2.10^{-3} M) in the presence of BF_{3}OEt_{2}. 

Yields (%) 

BF_{3}OEt_{2} (equiv./mol) 

0.00 0.05 0.10 0.15 0.20 0.25 0.30 

(a) 

Yields (%) 

BF_{3}OEt_{2} (equiv./mol) 

0.00 0.05 0.10 0.15 0.20 0.25 

(b)
CONCLUSION

To sum up, we have shown, as Lewis showed for coumarin\textsuperscript{66h} that complexation of the pyrone carboxyl of methoxy coumarins or psoralens induces an exciplex formation under irradiation. Only the singlet exciplex undergoes a reaction with an enhancement of the photochemical reactivity and of the stereoselectivity. We conclude that BF\textsubscript{3}OEt\textsubscript{2} is a catalyst for singlet excited state reactions and an inhibitor for triplet ones. \footnote{In ref. 6a and 6c Shim and coworkers showed by fluorescence quenching experiments that the photochemical reactivity of 3 is expected to be different from that of other coumarins.}
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[11] - Mantulin W.W., Song P.S., J. Am. Chem. Soc. (1973) 95, 5122-5121, in this work the authors have determined the phosphorescence/fluorescence ratio for 1, 2, hydroxycoumarin, 4 and 5 to 5.83, 0.05, 0.01, 11.85,13.05 respectively.


