Photocyclization of a Bichromophoric Phenol/Olefin System Substituted at the Methylene Spacer − Zwitterions versus H-Bridged Intermediates in the Excited State Proton Transfer

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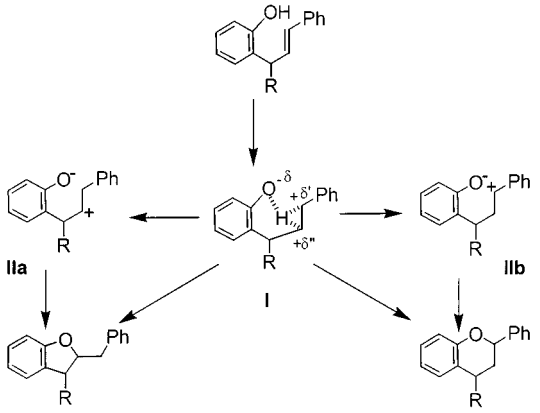
Photolysis of (*E*)- and (*Z*)-2-(1-ethyl-3-phenylpropenyl)-phenol (**1** and **2**) under a variety of conditions produces a mixture of dihydrobenzopyrans **3** and **4**, dihydrobenzofuran **5**, cyclopropanes **6** and **7**, and rearranged olefin **8**. Acidic treatment of **1** and **2** gives a mixture of the six-membered ring products **3** and **4**. Remarkable differences, associated with the nature of the precursor and the reaction conditions, are observed in the regiochemistry of cyclization and in the stereochemistry of the dihydrobenzopyrans (**3**/**4** ratio). This points in favour of an H-bridged intermediate, rather than a fully zwitterionic species, as the direct precursor of the photocyclized products.

Introduction

Cinnamylphenols are bichromophoric compounds containing phenol and styrene moieties connected through a methylene spacer. Their photochemical reactions have been investigated in some detail; photocyclization to dihydrobenzopyrans and dihydrobenzofurans has in most cases been interpreted in terms of a mechanism involving excited state proton transfer.[1−4] This mechanism, outlined in Scheme 1 for the parent compound (*E*)-2-(3-phenyl-2-propenyl)-phenol, would formally proceed through zwitterionic species (i.e., **IIa** and **IIb**). However, if such species (with full charge separation) were actual intermediates, the six-membered ring product should be overwhelmingly predominant due to the much higher stability expected for a benzylic cation. Notably, though, ring-closure to the five-membered ring product does occur to a significant extent.

On the other hand, it has been reported that irradiation of (*E*)-1,3-diphenylpropenes mainly affords the corresponding (*Z*) isomers.[5−8] This reactivity pattern is strongly modified by the presence of alkyl substituents at the C-3 position in the aliphatic chain, which favours the di-π-methane rearrangement as a competing reaction.[9,10] Excitation to higher singlet states in polar solvents enhances the di-π-methane pathway.[11]



Scheme 1. Photocyclization of (*E*)-2-(3-phenyl-2-propenyl)phenol through excited state proton transfer

In this context, we decided to perform a study on the photochemical behaviour of (*E*)- and (*Z*)-2-(1-ethyl-3-phenylpropenyl)phenol (**1** and **2**, respectively), each of which bears an ethyl substituent at the methylene spacer. Introduction of the substituent could result in di-π-methane rearrangement as an *alternative reaction pathway* and would, on the other hand, provide a marker for analysis of the *stereoselectivity* in the photocyclization processes. If fully zwitterionic intermediates were actually intervening, the same stereoisomeric ratio should be observed for the cyclized products irrespective of the (*Z*/*E*) stereochemistry of the starting cinnamylphenol. However, a certain degree of stereochemical memory would indicate that the proton was not completely transferred in the excited state, thus substantiating the involvement of species such as **I** (Scheme 1) as direct precursors of the final products.

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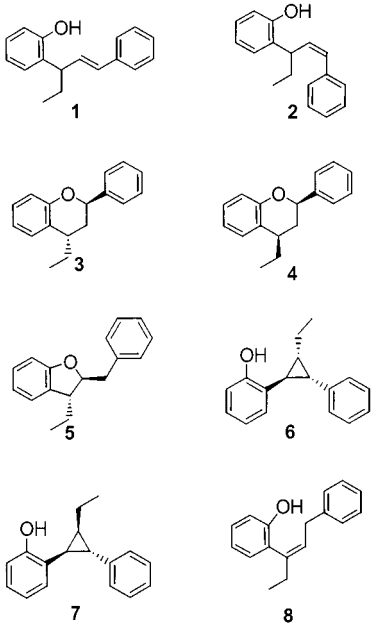
Results and Discussion

The required cinnamylphenols **1** and **2** (Scheme 2) were prepared as described in the literature.[12] The photochemistry of **1** was first investigated in cyclohexane at 254 nm (Table 1, Entry 1). Under these conditions, cyclization was the major process, to give **3**, **4**, and **5**. Small amounts of the isomeric olefins **2** and **8** were also formed. In addition, the cyclopropanes **6** and **7**, arising from di-π-methane rearrangement, were detected as minor products. Irradiation at longer wavelength (300 nm) in the same solvent (Table 1, Entry 2) resulted in only four products, the (*Z*) isomer **2** (major) and the cyclic ethers **3**, **4**, and **5**.



Scheme 2. Structures of compounds **1**−**8**

Thus, substitution at the methylene carbon atom resulted in the formation of minor amounts of rearranged cyclopropanes **6** and **7**; this type of products had not previously been observed in the irradiation of other cinnamylphenols. As in the case of related 1,3-diphenylpropenes, the chromophore involved must be the styrene substructure; the fact that these products appear only upon short-wavelength irradiation confirms that excitation to higher singlet states plays a key role in the process.[11]

It is remarkable that the two possible dihydrobenzopyrans **3** and **4** were obtained in significant amounts, although **4** was the major product. The (*Z*) stereochemistry of **4** was established by comparison of its spectroscopic data with those previously reported for the same compound.[13] The other isolated benzopyran was hence unambiguously assigned as the (*E*) isomer **3**. The **3**/**4** ratio did not change significantly with the irradiation wavelength. In contrast, only one of the two possible dihydrobenzofurans was observed; it was identified as the (*E*) isomer **5** on the basis of NOE experiments. This is not surprising, since formation of the (*Z*) isomer would be disfavoured due to steric hindrance.

The *trans*-1,2-diaryl structures of **6** and **7** were assigned on the basis of their NMR spectra, by comparison with those of other 1-alkyl-2,3-diphenylcyclopropanes.[14] NOE experiments were again used to assess the relative arrangement of the ethyl group with respect to the aromatic substituents.

Products **2** and **8** are the result of double bond isomerization. The (*E*)-to-(*Z*) phototransformation is usual in cinnamylphenols; however, migration of the double bond in these compounds has not been reported so far. Obviously, the higher degree of substitution in the resulting olefin due to the presence of the ethyl group could be the driving force for this reaction. The structure of **8** was unambiguously confirmed by comparison with an authentic sample obtained by an alternative synthesis: treatment of 2′-hydroxy-3-phenylpropiophenone with ethylmagnesium chloride, followed by treatment of the unisolated alcohol with HBr. Again, NMR spectroscopy, including NOE experiments, confirmed the (*Z*) arrangement of this olefin.

The product distribution upon irradiation at 254 nm was strongly affected by the solvent polarity. Irradiation in acetonitrile (Table 1, Entry 3) resulted in a dramatic enhancement of the di-π-methane photorearrangement (combined yield for **6** and **7** higher than 60%). In the same medium but with irradiation at 300 nm (Table 1, Entry 4), (*E*)/(*Z*) isomerization of the styrene double bond was the main process observed. The same was true for the acetone-photosensitised irradiation of **1**, which exclusively produced **2** (Table 1, Entry 5). This is consistent with the previously established mechanism, in which (*E*)/(*Z*) isomerization of cinnamylphenols is accepted to take place from the styrene triplet.[1]

Table 1. Irradiation of **1** and **2**

Entry	Substrate	Conditions	Conversion (%)	Product yields (%)						
				2 or **1**	**3**	**4**	**5**	**6**	**7**	**8**
1	**1**	C_6H_{12}, 254 nm	94	5	22	32	30	5	2	4
2	**1**	C_6H_{12}, 300 nm	44	52	14	19	15	–	–	–
3	**1**	CH_3CN, 254 nm	87	15	3	5	3	26	37	11
4	**1**	CH_3CN, 300 nm	43	81	3	2	–	6	8	–
5	**1**	$(CH_3)_2CO$, 300 nm	70	100	–	–	–	–	–	–
6	**2**	C_6H_{12}, 254 nm	76	10	27	22	33	4	2	1
7	**2**	CH_3CN, 254 nm	76	22	4	4	5	22	36	7

After completion of the photochemical studies with (*E*)-2-(1-ethyl-3-phenylpropenyl)phenol (**1**), the two photolysis experiments at 254 nm were also performed with the (*Z*) isomer **2**. Longer irradiation wavelengths were not used because the absorption of **2** under these conditions is very weak. As stated above, our aim was to ascertain whether the stereochemistry of the five- and six-membered ring products was dependent on the (*Z*)/(*E*) nature of the starting cinnamylphenol. As shown in Table 1 (Entry 6), irradiation of **2** in cyclohexane at 254 nm gave rise to **1** and **3**−**8**, with the cyclic ethers again being the major products. The most interesting observation was the **3/4** ratio, which was found in this case to be 1.23. Thus, when starting from **2**, the (*E*)-dihydrobenzopyran **3** predominates over its (*Z*) isomer **4**. This result is exactly the opposite of that reported above for **1** (Table 1, Entry 1), in which formation of **4** is favoured and the **3/4** ratio is 0.68. Irradiation of **2** in acetonitrile at 254 nm (Table 1, Entry 7) resulted in a product distribution similar to that obtained starting from **1**.

To make sure that the yields of the products were not reflecting secondary photochemical events (i.e., photolysis of **2** or any of the photoproducts), the **3/4** ratio was also determined after shorter irradiation times. The results obtained when starting from **1** and **2** are shown in Figure 1. It was found that the differences between the **3/4** ratios were even more important at lower degrees of conversion than upon prolonged irradiation, confirming the significance of the observed trends.

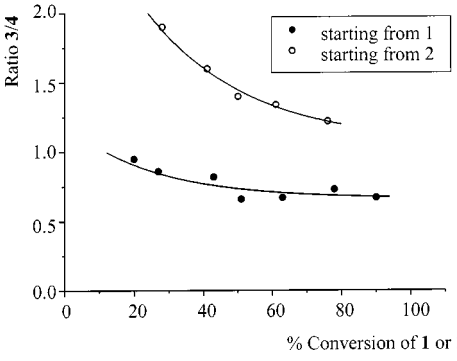


Figure 1. Stereoselectivity (**3/4** ratio) of the photocyclization of cinnamylphenols **1** and **2** to the six-membered ring products, at different degrees of conversion

Chemical cyclization of **1** and **2** was also achieved by treatment with HBr. Under these conditions, no dihydrobenzofuran was obtained. The only products were **3** and **4**, with a **3/4** ratio of 1.38, whether starting either from the (*E*)-propene or its (*Z*) counterpart. The absence of **5** in the reaction mixture was consistent with the preferred formation of the benzylic cation upon protonation of the double bond. On the other hand, the lack of any dependence of the **3/4** ratio on the (*Z*)/(*E*) stereochemistry of the starting olefin agreed well with the planar arrangement expected for carbocations. The divergent behaviour observed in the photochemical and in the chemical processes points to the involvement of different intermediates. As a consequence, the results shown in Table 1 cannot be satisfactorily explained on the basis of the generation of long-lived zwitterions such as **IIa** and **IIb** (Scheme 1). If such species (with full charge separation) were the key intermediates, the photolysis results would be very similar to those obtained in the acid-catalysed cyclization, which is clearly not the case. Thus, although the involvement of shorter-lived zwitterions cannot be completely ruled out, direct cyclization of a bridged entity such as **I** with a certain degree of charge development at the oxygen (−δ) and the originally olefinic carbon atoms (+δ′ and +δ′′) appears more consistent with the experimental observations. The residual π-bonding of **I** would justify the different stereoselectivities (**3/4** ratio) observed in the 6-*endo*-*trig*[15] photocyclization of the two (*E*)/(*Z*) isomers **1** and **2**.

Conclusions

Upon introduction of an ethyl substituent at the methylene spacer of the 2-cinnamylphenol system, the di-π-methane rearrangement occurs as an additional photochemical reaction pathway. On the other hand, the stereochemistry of the dihydrobenzopyrans obtained in the presence of this substituent points in favour of an H-bridged intermediate, rather than a fully zwitterionic species, as the direct precursor of the photocyclized products.

Experimental Section

General: FTIR spectra were obtained in CCl_4 solution; $\tilde{\nu}_{max}$ [cm^{-1}] are given for the main absorption bands. ^1H NMR spectra were measured in $CDCl_3$ with a 300 MHz instrument; chemical shifts are reported in δ [ppm], with TMS as internal standard. Mass spectra were obtained by electron impact; the *m*/*z* ratio and the relative intensities (%) are indicated for selected peaks.

Irradiation Procedure: Compounds **1** and **2** were prepared by a known procedure.[12] Solutions of **1** or **2** (5 mM) in cyclohexane, acetonitrile or acetone were irradiated in a multilamp photoreactor with the light of four 8 W lamps emitting mainly at 254 or 300 nm, through quartz or Pyrex, respectively. The course of the reaction was monitored by GC, GC-MS and ^1H NMR; the degrees of conversion, the product distributions and the mass balances were determined by use of suitable standards. Isolation and purification were performed by conventional column chromatography on 60 PF_{254} silica gel with dichloromethane as eluent and subsequent HPLC with a semipreparative column, with hexane/ethyl acetate as eluent (isocratic mode). The degrees of purity of the isolated photoproducts were assessed by GC and HPLC, single peak-chromatograms being obtained in all cases.

Alternative Synthesis of Compound 8: A solution of 2′-hydroxy-3-phenylpropiophenone (2.0 g, 8.8 mmol) and ethylmagnesium chloride (18.0 mmol) in anhydrous ether was refluxed for 2 h under Ar. The mixture was then poured onto crushed ice (100 g), and hydrochloric acid (35%, 2 mL) was added. The organic layer was removed and the aqueous solution was extracted with ether (3 × 50 mL). The combined ethereal solutions were dried and the solvents were evaporated to afford a residue, which was treated with concentrated HBr (5 mL) at room temperature for 1 h. Water (50 mL) was

then added and the solution was extracted with dichloromethane (3 × 50 mL). After drying with $MgSO_4$, the solvent was evaporated to give 1.9 g of a viscous oil. A 100 mg aliquot of this oil was purified by column chromatography and subsequently by HPLC, to afford 20 mg of pure **8**.

(*E*)-4-Ethyl-2-phenyl-2*H*-1-benzopyran (3): FTIR: $\tilde{\nu}$ = 3068, 3035, 2963, 2929, 2875, 1609, 1581, 1485, 1454, 1261, 1237. ^{1}H NMR: δ = 1.05 (t, ^1J = 7.4 Hz, 3 H, CH_3), 1.80 (m, 2 H, CHCH_2CH), 2.10 (m, 2 H, CH_2CH$_3$), 2.73 (m, 1 H, C*H*Ph), 5.10 (dd, ^1J = 6.5, ^2J = 7.3 Hz, 1 H, CH_2C*H*CH_2), 6.85−7.50 (m, 9 H, ArH). MS: *m*/*z* (%) = 238 (22) [M$^+$], 209 (100), 131 (19), 115 (31), 91 (37), 77 (16). Exact mass calcd. for $C_{17}H_{18}O$ 238.1358, found 238.1368.

(*E*)-2-Benzyl-3-ethyl-2,3-dihydrobenzofuran (5): FTIR: $\tilde{\nu}$ = 2692, 2929, 1611, 1596, 1493, 1478, 1461, 1231. ^{1}H NMR: δ = 0.85 (t, ^1J = 7.0 Hz, 3 H, CH_3), 1.60 (m, 2 H, CH_2CH$_3$), 2.90 (dd, ^1J = 6.4, ^2J = 13.8 Hz, 1 H, CH_2Ph), 3.10 (m, 2 H, C*H*CH_2CH$_3$ + CH_2Ph), 4.65 (m, 1 H, OC*H*), 6.70−7.40 (m, 9 H, ArH). MS: *m*/*z* (%) = 238 (21) [M$^+$], 147 (61), 131 (10), 91 (100), 77(8); Exact mass calcd. for $C_{17}H_{18}O$ 238.1358, found 238.1358.

2-(*trans*-2-Ethyl-*trans*-3-phenylcyclopropyl)phenol (6): FTIR: $\tilde{\nu}$ = 3609, 3573, 3066, 3029, 2962, 2930, 1605, 1586, 1490, 1460, 1259. ^{1}H NMR: δ = 1.00 (m, 3 H, CH_3), 1.55 (m, 3 H, C*H*CH_2CH$_3$), 2.10 (t, ^1J = 5.4 Hz, 1 H, C*H*C$_6$H$_4$OH), 2.25 (m, 1 H, C*H*Ph), 5.20 (s, 1 H, OH), 6.70−7.40 (m, 9 H, ArH). MS: *m*/*z* (%) = 238 (37) [M$^+$], 209 (100), 147 (32), 131 (18), 115 (25), 91 (37), 77(10). Exact mass calcd. for $C_{17}H_{18}O$ 238.1358, found 238.1358.

2-(*cis*-2-Ethyl-3-*trans*-phenylcyclopropyl)phenol (7): FTIR: $\tilde{\nu}$ = 3609, 3573, 3066, 3029, 2962, 2930, 1605, 1583, 1490, 1460, 1259. ^{1}H NMR: δ = 1.00 (t, ^1J = 7.0 Hz, 3 H, CH_3), 1.10−1.50 (m, 3 H, C*H*CH_2CH$_3$), 2.18 (t, ^1J = 7.6 Hz, 1 H, C*H*Ph), 2.40 (dd, ^1J = 7.6, ^2J = 12.0 Hz, 1 H, C*H*C$_6$H$_4$OH), 5.20 (s, 1 H, OH), 6.80−7.35 (m, 9 H, ArH). MS: *m*/*z* (%) = 238 (45) [M$^+$], 209 (100), 147 (50), 131 (27), 115 (48), 91 (50), 77(14). Exact mass calcd. for $C_{17}H_{18}O$ 238.1358, found 238.1357.

(*E*)-2-(1-Ethyl-3-phenyl-1-propenyl)phenol (8): FTIR: $\tilde{\nu}$ = 3526, 3028, 2927, 2855, 1644, 1486, 1453, 1195. ^{1}H NMR: δ = 1.00 (t, ^1J = 7.4 Hz, 3 H, CH_3), 2.35 (q, ^1J = 7.4 Hz, 2 H, CH_2CH$_3$), 3.20 (d, ^1J = 7.5 Hz, 2 H, CH_2Ph), 5.12 (s, 1 H, OH), 5.90 (t, ^1J = 7.5 Hz, 1 H, C=C*H*CH_2), 6.90−7.40 (m, 9 H, ArH). MS: *m*/*z* (%) = 238 (36) [M$^+$], 209 (50), 147 (48), 131 (34), 115 (16), 107 (27), 91 (100), 77 (20). Exact mass calcd. for $C_{17}H_{18}O$ 238.1358, found 238.1355.

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[1] M. C. Jiménez, F. Márquez, M. A. Miranda, R. Tormos, *J. Org. Chem.* **1994**, *59*, 197−202.
[2] M. C. Jiménez, M. A. Miranda, R. Tormos, *Tetrahedron* **1997**, *53*, 14729−14736.
[3] M. C. Jiménez, M. A. Miranda, R. Tormos, *J. Org. Chem.* **1998**, *63*, 1323−1326.
[4] M. T. Bosch-Montalvá, L. R. Domingo, M. C. Jiménez, M. A. Miranda, R. Tormos, *J. Chem. Soc., Perkin Trans. 2* **1998**, 2175−2179.
[5] S. S. Hixson, *J. Am. Chem. Soc.* **1972**, *94*, 2505−2507.
[6] S. S. Hixson, *J. Am. Chem. Soc.* **1972**, *94*, 2507−2508.
[7] S. S. Hixson, P. S. Mariano, H. E. Zimmerman, *Chem. Rev.* **1973**, *73*, 531−551.
[8] H. E. Zimmerman, D. Armesto, *Chem. Rev.* **1996**, *96*, 3065−3112.
[9] H. E. Zimmerman, T. R. Welter, *J. Am. Chem. Soc.* **1978**, *100*, 4131−4145.
[10] F. D. Lewis, X. B. Zuo, R. S. Kalgutkar, M. A. Miranda, E. Font-Sanchis, J. Perez-Prieto, *J. Am. Chem. Soc.* **2000**, 8571−8572.
[11] M. C. Jiménez, M. A. Miranda, R. Tormos, *Chem. Commun.* **2000**, 2341−2342.
[12] A. Alberola, A. González-Ortega, R. Pedrosa, M. Vicente, *Synthesis* **1984**, 238−240.
[13] T. Inoue, S. Inoue, K. Sato, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1647−1652.
[14] M. A. Miranda, J. Pérez-Prieto, E. Font-Sanchis, K. Kónya, J. C. Scaiano, *J. Org. Chem.* **1997**, *62*, 5713−5719.
[15] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

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