

## Enantioselective Discrimination in the Intramolecular Quenching of an Excited Aromatic Ketone by a Ground-State Phenol

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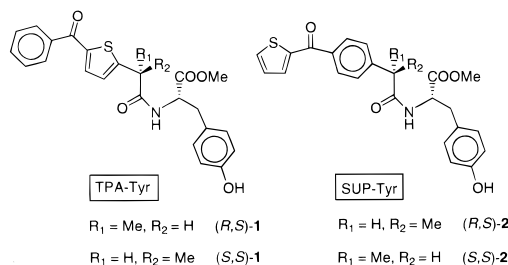
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Chiral recognition is a subject of increasing interest in photochemistry.<sup>1</sup> In principle, this can be achieved with optically active photosensitizers if an enantiodifferentiating interaction occurs in the relevant excited state. Photosensitized electron transfer processes appear specially suitable for such purposes, as the donor and the acceptor must form a highly coupled system for some time.<sup>2</sup> The use of chiral compounds as both excited sensitizers and quenchers could enable examination of pure chiral discrimination through comparison of the quenching rates, since enantiomers have otherwise the same electronic nature and the same size. Leigh et al.<sup>3</sup> have suggested that hydrogen abstraction from phenols by carbonyl  $\pi,\pi^*$  triplets involves electron transfer within a hydrogen-bonded triplet exciplex, followed by proton transfer. In this context, we have prepared bichromophoric compounds containing enantiomerically pure aryl ketones and phenols, to check the stereochemical aspects of intramolecular electron transfer by means of laser flash photolysis studies.

Benzoylthiophene is a heterocyclic diaryl ketone with a lowest lying  $\pi,\pi^*$  triplet.<sup>4</sup> This excited state involves predominantly the thenoyl chromophore; it has an energy<sup>4</sup> of ca. 63 kcal mol<sup>-1</sup> and is able to react with phenols, such as *p*-cresol and tyrosine methyl ester.<sup>5</sup> Both substructures are present in the four enantiomerically pure bichromophoric compounds prepared in this work: TPA-Tyr [(*R,S*)-1, (*S,S*)-1] and SUP-Tyr [(*R,S*)-2, (*S,S*)-2] (Scheme 1). We have studied the intramolecular electron-transfer process by laser flash photolysis through phenol quenching of the ketone triplet state and found a high degree of stereoselectivity, which agrees with a geometry where interaction between the  $\pi$ -systems of the phenol and the aromatic ketone is maximized.

Compounds **1** and **2** differ in the relative aromatic ketone versus phenol orientation. They were obtained by condensation of the

### Scheme 1



corresponding racemic acid, tiaprofenic acid (TPA) or suprofen (SUP), with the methyl ester of the natural occurring amino acid (*S*)-tyrosine, in the presence of a carbodiimide {(1-ethyl-3-[3-dimethylamino]propylcarbodiimide), EDC}. In both cases, after purification of the resulting amides, one of the diastereoisomers crystallized. The other stereoisomers were further purified by HPLC chromatography [potassium dihydrogen phosphate (0.06 M):acetonitrile:triethylamine (317:183:0.1 by volume)]. All the bichromophoric compounds were fully characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and elemental analysis.

Neither the UV absorption spectra nor the infrared spectra in solution were indicative of ground-state complexation between the carbonyl group and the remote phenolic moiety in these compounds. However, the <sup>1</sup>H NMR spectra in CDCl<sub>3</sub> clearly displayed shielding of some aromatic protons; the most significant effect was observed at the position *meta* to the Tyr OH group. For instance, the  $\delta$  values for (*S,S*)- and (*R,S*)-TPA-Tyr were 6.68 and 6.76 ppm, respectively. For comparison, the corresponding proton of Tyr methyl ester appears at 6.95 in the same solvent. Interestingly, when <sup>1</sup>H NMR spectra were recorded in CD<sub>3</sub>OD the  $\delta$  value was the same in the three compounds (6.88 ppm).

In the case of SUP-Tyr, the X-ray structures could be unambiguously determined for both diastereoisomers.<sup>6,7</sup> The configuration of the less soluble isomer in chloroform was found to be (*R,S*) (Figure 1). A similar distance between the OH of the phenol and the C=O of the ketone chromophores (1.903 Å for the (*R,S*) isomer and 1.937 Å for the (*S,S*) isomer) was found in the solid state for both isomers. However, the angles between the planes of the aromatic rings connected through the aliphatic chain were somewhat different (18.9 and 24.5°, respectively).

We were able to obtain good crystals from only one of the stereoisomers of TPA-Tyr. Its structure was unambiguously determined as (*S,S*) by X-ray analysis, showing as in the case of SUP-Tyr a short distance OH...CO (1.950 Å); the angle between the planes of phenoxy and the thienyl group was 16.6°. Modeling studies<sup>8</sup> were done for both TPA-Tyr diastereoisomers and, as in the case of SUP-Tyr, they present a similar distance between the

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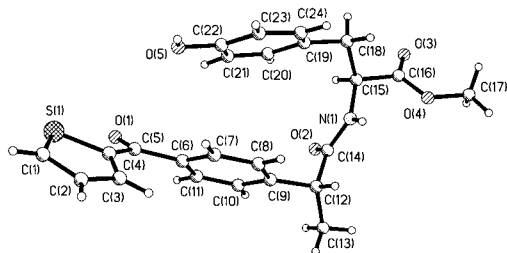
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(6) Compound (*R,S*)-2: C<sub>24</sub>H<sub>23</sub>NO<sub>5</sub>S, *M* = 437.49, triclinic, space group *P*1, *a* = 7.902(2) Å, *b* = 8.256(3) Å, *c* = 8.859(3) Å,  $\alpha$  = 78.40(2)°,  $\beta$  = 76.73(2)°,  $\gamma$  = 87.96(3)°, *V* = 551.0(3) Å<sup>3</sup>, *Z* = 1, *D*<sub>c</sub> = 1.318 g cm<sup>-3</sup>,  $\lambda$ (Mo K $\alpha$ ) = 0.71069 Å, *T* = 293(2) K,  $\mu$ (Mo K $\alpha$ ) = 0.182 mm<sup>-1</sup>. A well-shaped crystal of dimensions 0.18 × 0.20 × 0.20 mm was mounted on a Siemens P4 diffractometer. A total of 2886 independent reflections were collected. The structure was solved by direct methods and refined by full-matrix least-squares analysis on *F*<sup>2</sup> (SHELXTL). The refinement converged to *R*<sub>1</sub> = 0.033 [*F* > 4 $\sigma$ (*F*)], *wR*<sub>2</sub> = 0.137 (all data), and *GOF* = 0.89. Absolute structure parameter = 0.05(6).

(7) Compound (*S,S*)-2: C<sub>24</sub>H<sub>23</sub>NO<sub>5</sub>S, *M* = 437.49, triclinic, space group *P*1, *a* = 8.056(5) Å, *b* = 8.326(5) Å, *c* = 8.751(6) Å,  $\alpha$  = 77.78(5)°,  $\beta$  = 78.13(5)°,  $\gamma$  = 89.88(5)°, *V* = 560.9(6) Å<sup>3</sup>, *Z* = 1, *D*<sub>c</sub> = 1.295 g cm<sup>-3</sup>,  $\lambda$ (Mo K $\alpha$ ) = 0.71069 Å, *T* = 293(2) K,  $\mu$ (Mo K $\alpha$ ) = 0.179 mm<sup>-1</sup>. A well-shaped crystal of dimensions 0.18 × 0.19 × 0.24 mm was mounted on a Siemens P4 diffractometer. A total of 2482 independent reflections were collected. The structure was solved by direct methods and refined by full-matrix least-squares analysis on *F*<sup>2</sup> (SHELXTL). The refinement converged to *R*<sub>1</sub> = 0.049 [*F* > 4 $\sigma$ (*F*)], *wR*<sub>2</sub> = 0.132 (all data), and *GOF* = 1.12. Absolute structure parameter = 0.02(11).



**Figure 1.** Molecular structure of *(R,S)*-2.

**Table 1.** Lifetimes and Rate Constants for Intramolecular Quenching of the Triplet States of Bichromophoric Compounds 1–3<sup>a</sup>

compd	solvent	lifetime $\tau$ (ns)	$k_{ET}^b$ ( $10^5$ s <sup>-1</sup> )
<i>(R,S)</i> -1	MeOH	302	30
	CH <sub>2</sub> Cl <sub>2</sub>	30	330
<i>(S,S)</i> -1	MeOH	52	189
	CH <sub>2</sub> Cl <sub>2</sub>	12	830
<i>(R,S)</i> -2	MeOH	45	219
	CH <sub>2</sub> Cl <sub>2</sub>	5	1996
<i>(S,S)</i> -2	MeOH	312	29
	CH <sub>2</sub> Cl <sub>2</sub>	10	996
<i>(R,S)</i> -3	MeOH	2800	— <sup>c</sup>
<i>(S,S)</i> -3	MeOH	1400	0.4
2-benzoylthiophene	<sup>d</sup> MeOH	2800	— <sup>e</sup>
	CH <sub>2</sub> Cl <sub>2</sub>	3970	— <sup>e</sup>

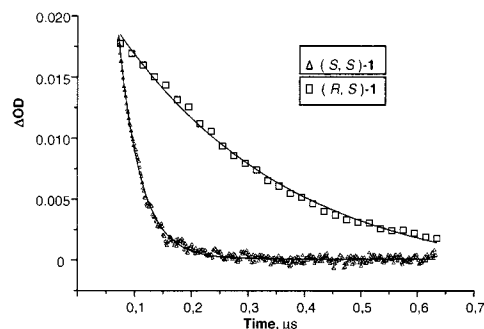
<sup>a</sup> Concentrations:  $8 \times 10^{-4}$  M for 1–2 and  $7 \times 10^{-4}$  M for 3. Under these conditions, (bimolecular) self-quenching can contribute no more than about 10% to the measured triplet lifetimes. <sup>b</sup> Electron-transfer rate constants are obtained by using the equation  $k_{ET} = 1/\tau_1 - 1/\tau_2$ , where  $\tau_1$  and  $\tau_2$  are the lifetimes of the ketone triplets in the bichromophoric compound and 2-benzoylthiophene, respectively. <sup>c</sup> No significant intramolecular quenching observed. <sup>d</sup> Concentration:  $5 \times 10^{-4}$  M. <sup>e</sup> The intermolecular quenching constant by Tyr methyl ester was  $2.0 \times 10^8$  M<sup>-1</sup> s<sup>-1</sup> in MeOH and  $2.4 \times 10^9$  M<sup>-1</sup> s<sup>-1</sup> in CH<sub>2</sub>Cl<sub>2</sub>. With anisole (as model for the methylated compounds 3) no significant intermolecular quenching was observed.

carbonyl and the phenol groups, as well as some differences in the angles between the planes of the aromatic rings connected through the peptidic chain. It is remarkable that the calculated and determined (X-ray) structures for stereoisomer *(S,S)*-TPA-Tyr were in excellent agreement. The energy difference between the folded and extended minima was found to be 2.6 kcal mol<sup>-1</sup>.

Dynamic studies on the photobehavior of bichromophoric compounds 1 and 2 in methanol and dichloromethane ( $8 \times 10^{-4}$  M) were performed using a 355 nm laser (Nd:YAG). Transients with absorption maxima at ca. 370 and 580 nm were observed in all cases; they can be assigned to the expected ketone triplets. Their lifetimes were higher in methanol than in dichloromethane (Table 1). This effect can be attributed to the possibility of hydrogen bond with the solvent.

The transients generated in methanol upon laser excitation of the *(R)*- or *(S)*-TPA chromophore were quenched quite differently by the *(S)*-tyrosine moiety ( $k_{ET(R,S)} = 30 \times 10^5$  s<sup>-1</sup> and  $k_{ET(S,S)} = 189 \times 10^5$  s<sup>-1</sup>) (Figure 2). Thus, the electron-transfer rate constants ratio was ca. 6. Similarly, for the bichromophoric compounds *(R,S)*-SUP-Tyr and *(S,S)*-SUP-Tyr the electron-transfer rate constants were  $k_{ET(R,S)} = 219$  s<sup>-1</sup> and  $k_{ET(S,S)} = 29$  s<sup>-1</sup>, with a ratio of ca. 8. The same trend was observed in dichloromethane. For comparative purposes, the triplet lifetimes of the nonphenolic methoxy analogues *(R,S)*- and *(S,S)*-3 were

(8) Structure minimization was carried out using Mechanics as provided in the CAChe System Version 3.1 (Oxford Molecular Ltd., 1997). The molecular geometries of the minimum energy conformations were obtained using optimization routine.



**Figure 2.** Molecular structure of *(S,S)*-2.

also measured. The intramolecular quenching was much slower, but still some chiral recognition was observed. The lifetime of the model ketone 2-benzoylthiophene and the bimolecular quenching constants are also given in Table 1 for comparison. The high stereoselectivity for these processes is suggestive of more highly ordered exciplex intermediates for *(S,S)*-1 and *(R,S)*-2 than for their corresponding diastereoisomers. These data agree well with the relative ability of the systems to get a parallel arrangement of the aromatic rings connected through the aliphatic chain (see above). It is interesting to note that the triplet lifetime of *(R,S)*-1 is shorter than that of *(S,S)*-2, in which the stereochemistry is the same but the ring to which the phenolic substituent is attached varies between the 2-thiophenyl and phenyl rings. The same applies to the comparison between *(S,S)*-1 and *(R,S)*-2. This could be attributed to the fact that in the lowest ( $\pi$ ,  $\pi^*$ ) triplet of 2-benzoylthiophene, electron density is lower in the thiophenyl ring than in the phenyl ring because of the strong charge-transfer character of the lowest triplet state.

It appears that the ability of the system to form the hydrogen-bonded exciplex and hence the rate of intramolecular electron transfer strongly depends on the nonbonding electronic interactions between the aromatic  $\pi$ -systems. Small deviations from the parallelism are associated with a dramatic decrease of the interchromophoric electron-transfer quenching rates. Finally, a clear deuterium isotope effect was observed in CH<sub>3</sub>OD (for instance, in the case of *(R,S)*-1  $k_H/k_D$  was ca. 1.5), which could be indicative of phenolic hydrogen abstraction being the rate determining process leading to deactivation of the triplet state.<sup>3</sup>

In summary, laser-flash photolysis experiments have proven chiral recognition in the intramolecular electron transfer from the phenolic moiety to the ketone chromophore. This could have important biological consequences. Thus, tiaprofenic acid and suprofen have been shown to be potent photoallergens. This is believed to depend on the photochemical binding of the drugs to proteins, where the key sites seem to be the tyrosine units.<sup>5</sup> Hence, the bichromophoric compounds TPA-Tyr and SUP-Tyr could be suitable models to reproduce the drug–protein preassociated complexes. The remarkable configuration-dependent photobehavior found in the present work suggests the possibility of a different photoallergenic potential for the drug enantiomers.

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**Supporting Information Available:** Tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates; molecular structure of *(S,S)*-2 and transient absorption spectrum obtained upon laser flash photolysis of TPA-Tyr (*(R,S)*-1 (PDF). X-ray crystallographic file for *(S,S)*-1, *(R,S)*-2, and *(S,S)*-2 in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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