ORGANIC LETTERS

2004
Vol. 6, No. 22
3905−3908

Diels−Alder Reaction between Indoles and Cyclohexadienes Photocatalyzed by π,π^* Aromatic Ketones

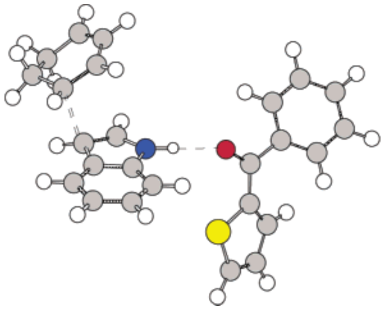
Julia Pérez-Prieto,*,[†] Salah-Eddine Stiriba,[†] María González-Béjar,[†] Luis R. Domingo,[†] and Miguel A. Miranda*,[‡]

Departamento de Química Orgánica/ICMOL, Universidad de Valencia,
Av. Vicent Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain, and
Departamento de Química/Instituto de Tecnología Química UPV-CSIC,
Universidad Politécnica de Valencia, Camino de Vera s/n, 46071 Valencia, Spain

julia.perez@uv.es

Received July 28, 2004

ABSTRACT



Diels–Alder reactions between indoles and cyclohexadienes can be photocatalyzed by benzoylthiophenes. Both experimental and theoretical studies show that the reactions occur through ternary excited triplet state complexes (triplet triplexes).

In general, the Diels−Alder reaction is inefficient when both diene and dienophile components are electron-rich compounds.[1] However, several strategies have been devised to overcome this limitation,[2−5] including photosensitization by cyanoarenes in solvents of low polarity,[4] where the reaction proceeds through intermediate ternary excited-state complexes (triplexes).[6] These triplexes arise from diene trapping of the exciplexes formed between the sensitizer-excited singlet states and the ground-state dienophiles. Side reactions become significant when the excited cyanoarene is quenched by the diene or when the exciplex decays irreversibly before trapping.

On the other hand, electron-transfer catalysis promotes [4 + 2] cross-cycloadditions between reactants with similar HOMO energies, via electrochemically, chemically, or photochemically generated radical cations.[2,3,5,7] Thus, in the electron-transfer from indoles to photoexcited triarylpyrylium

---

* To whom correspondence should be addressed.

[†] Universidad de Valencia.

[‡] Universidad Politécnica de Valencia.

(1) An interesting exception is the Diels−Alder reaction between C_{60} and Danishefsky's dienes: Mikami, K.; Matsumoto, S.; Okubo, Y.; Fujitsuka, M.; Ito, O.; Suenobu, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **2000**, *122*, 2236.

(2) (a) Mattay, J.; Trampe, G.; Runsink, J. *Chem. Ber.* **1988**, *121*, 1991. (b) Mattay, J.; Vondenhof, M.; Denig, R. *Chem. Ber.* **1989**, *122*, 951.

(3) (a) Pabon, R. A.; Bellvile, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1983**, *105*, 5158. (b) Schmittel, M.; von Seggern, H. *J. Am. Chem. Soc.* **1993**, *115*, 2165. (c) Bauld, N. L.; Yang, J.; Gao, D. *J. Chem. Soc., Perkin Trans. 2* **2000**, 207.

(4) (a) Calhoun, G. C.; Schuster, G. B. *Tetrahedron Lett.* **1986**, *27*, 911. (b) Akbulut, N.; Hartsough, D.; Kim, J. I.; Schuster, G. B. *J. Org. Chem.* **1989**, *54*, 2549. (c) Kim, J. I.; Schuster, G. B. *J. Am. Chem. Soc.* **1992**, *114*, 9309.

(5) (a) Gieseler, A.; Steckhan, E.; Wiest, O.; Knoch, F. *J. Org. Chem.* **1991**, *56*, 1405. (b) Wiest, O.; Steckhan, E. *Tetrahedron Lett.* **1993**, *34*, 6391.

(6) The formation and behavior of fluorescent exciplexes and triplexes has been reported in the literature: Lewis, F. D.; Li, L.-S.; Kurth, T. L.; Kalgutkar, R. S. *J. Am. Chem. Soc.* **2000**, *122*, 8573.

(7) Mlcoch, J.; Steckhan, E. *Tetrahedron Lett.* **1987**, *28*, 1081.

10.1021/ol048520c CCC: $27.50

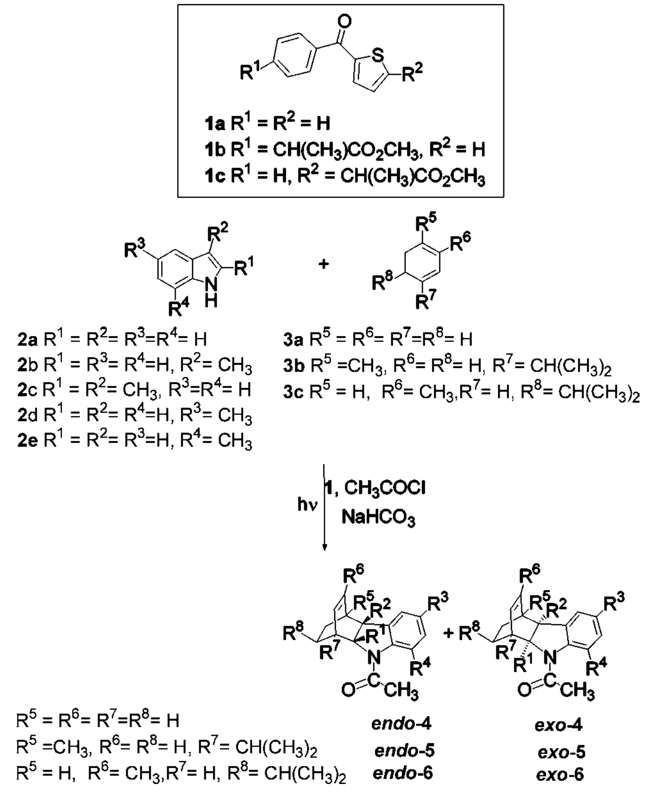
salts, the efficiencies of fluorescence quenching correlate well with the indoles' oxidation potentials. The resulting indolyl radical cations can react with cyclohexadienes, leading to tetrahydroethanocarbazoles.[5] Theoretical and experimental studies agree with a stepwise mechanism for the cycloaddition process that is initiated by diene attack to the 3-position of the indole radical cation.[8]

Up to now, attempts to achieve [4 + 2] cross-cycloaddition between two electron-rich components promoted by the usual triplet sensitizers (i.e., benzophenone) have been unsuccessful, leading mainly to dimerization of the dienes through a triplet−triplet energy transfer process.[2,4] Herein, we describe the Diels−Alder reaction of a series of indoles with 1,3-dienes photocatalyzed by π,π^* aromatic ketones. Although diene dimerization is also observed, the results provide a novel method for promoting the [4 + 2] cross-cycloaddition reaction between electron-rich components. Experimental and theoretical studies agree well with the involvement of triplet ketone-indole exciplexes,[9] which are quenched by the diene to afford intermediate triplexes, leading to the Diels−Alder cycloadducts as final products.

We have recently shown that 2-benzoylthiophene (BT; π,π^* triplet) is quenched by indole (InH) in solvents of different polarity.[10] Time-resolved techniques have shown that the BT triplet (λ_{max} at 350 and 600 nm) is converted with quantum yield close to 1 into the BT ketyl radical (λ_{max} at 350 and 580 nm) and indolyl radical (λ_{max} at 320 and 510 nm). However, low conversions of the starting reagents are obtained upon prolonged irradiation, indicating that recombination within the radical pairs must occur to a large extent, regenerating the starting materials. Solvent-dependence of the quenching rate constants, together with density functional theoretical (DFT) calculations, agree with hydrogen abstraction occurring by a mechanism where electron transfer precedes proton transfer in a hydrogen-bonded BT···HIn exciplex. As this exciplex exhibits significant charge separation, the electron-rich character of its indole component is greatly reduced. Hence, it would be feasible to use BT···HIn triplet exciplexes as dienophile components in Diels−Alder reactions, in processes that would actually involve ternary excited triplet state complexes ("triplet triplexes"). To our knowledge, this possibility has not yet been explored. Along this line, the aim of the present work has been to investigate whether the Diels−Alder reaction between indoles and cyclohexadienes can be photocatalyzed by 2-benzoylthiophenes. The results, although not yet optimized, are interesting as a proof of the concept.

Product studies were performed after irradiation (UVA lamp emitting at 400 ≥ λ ≥ 320 nm) of deaerated dichloromethane solutions of BT (**1a**, 0.005 mmol), InH (**2a,** 0.1 mmol), and 1,3-cyclohexadiene (CHD, **3a**, 0.2 mmol) for 6 h.[11] To avoid possible secondary reactions of the cycloadducts, an acetylation reagent (acetyl chloride/NaHCO$_3$) was also added.[5] Indeed, the Diels−Alder products **4a** were obtained in 15% yield (1.5:1 *endo*:*exo* ratio) (Scheme 1 and run 1 in Table 1). Control experiments showed that *N*-acetylindole was not formed under the reaction conditions. Besides, irradiation of *N*-acetylindole and CHD in the presence of the sensitizer did not give **4a**. Energy transfer from the BT π,π^* triplet excited state (E_T = 63 kcal/mol)[12] to **3a** (E_T = 52 kcal/mol)[13] led to CHD dimers

Scheme 1. Diels−Alder Reaction Photocatalyzed by 2-Benzoylthiophenes



---

[8] (a) Haberl, U.; Steckhan, E.; Blechert, S.; Wiest, O. *Chem. Eur. J.* **1999**, *5*, 2859. (b) Saettel, N. J.; Singleton, D. A.; Meyer, M. P. *J. Am. Chem. Soc.* **2002**, *124*, 11552.

[9] Triplet exciplexes between photoexcited quinones and aromatic donors have been observed directly by time-resolved picosecond spectroscopy: Rathore, R.; Hubig, S. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 11468.

[10] Pérez-Prieto, J.; Boscá, F.; Galian, R. E.; Lahoz, A.; Domingo, L. R.; Miranda, M. A. *J. Org. Chem.* **2003**, *68*, 5104.

[11] **Standard Procedure for the Diels−Alder Reactions.** To a deaerated dichloromethane solution of InH (0.1 mmol), CHD (0.2 mmol), and powdered NaHCO$_3$ (18 mg), acetyl chloride (0.1 mmol) and later BT (0.005 mmol) were added under nitrogen atmosphere. After irradiation water was added, and the organic phase was separated and dried (Na$_2$SO$_4$). The solvent was evaporated, and the crude was analyzed by ^{1}H NMR. The products were isolated by column chromatography (polarity from hexane/ethyl acetate 7:1 to pure ethyl acetate) and further purified by HPLC (hexane/ethyl acetate/dichoromethane 7:1:1). ***endo*-4b**: ^{1}H NMR (300 MHz) δ 1.2−1.3 (m, 2H), 1.4 and 1.5 (2s, 3H) 2.3 and 2.4 (2s, 3H), 2.6−2.7 and 3.0 (m and bb, 2H), 3.8 and 4.2 (2s, 1H), 5.9−6.0 (m, 2H), 6.9−7.2 (m, 5H), 8.1 (d, J = 6.0 Hz, 1H). ***exo*-4b**: ^{1}H NMR (300 MHz): δ 1.2−1.3 (m, 2H), 1.25 and 1.3 (2s, 3H), 2.15 and 2.2 (2s, 3H), 2.5−2.6 and 2.8 (m and bb, 2H), 3.6 and 4.0 (2bb, 1H), 6.2−6.5 (m, 2H), 6.9−7.2 (m, 5H), 8.2 (d, J = 8.1 Hz, 1H). ***endo*-4d**: ^{1}H NMR (300 MHz) δ 1.2−1.5 (m, 2H), 1.6−1.8 (m, 2H), 2.3 and 2.4 (2s, 6H), 2.9−3.1 and 3.4 (m and bb, 2H), 3.6 and 3.7 (2dd, J_1 = 9.1 Hz, J_2 = 2.6 Hz, 1H), 4.4 and 4.6 (2dd, J_1 = 9.1 Hz, J_2 = 2.6 Hz, 1H), 5.9−6.2 (m, 2H), 6.9−7.1 (m, 3H), 8.0 (d, J = 7.8 Hz, 1H). ***exo*-4d**: ^{1}H NMR (300 MHz) δ 0.9−1.2 (m, 4H), 2.3 and 2.3 (2s, 6H), 2.7−3.0 and 3.3 (m and bb, 2H), 3.5 and 3.5 (2dd, J_1 = 10.5 Hz, J_2 = 3.9 Hz, 1H), 4.2 and 4.5 (2dd, J_1 = 10.8 Hz, J_2 = 1.5 Hz, 1H), 6.2−6.6 (m, 2H), 6.9 and 7.0 (m, 3H), 8.1 (d, J = 8.1 Hz, 1H).

[12] Arnold, D. R.; Birtwell, R. J. *J. Am. Chem. Soc.* **1973**, *95*, 4599.

Table 1. Diels–Alder Reaction between Indoles and Cyclohexadienes Photosensitized by 2-Benzoylthiophenes in Dichloromethane

run	sensitizer	indole	diene	CHD-dimers yield (%)	Diels–Alder yield (%)[a]	*endo/exo*
1	**1a**	**2a**	**3a**	38	**4a**[5a] (15)	1.5:1.0
2	**1a**		**3a**	99		
3	**1b**	**2a**	**3a**	27	**4a** (14)	1.4:1.0
4	**1c**	**2a**	**3a**	23	**4a** (14)	1.7:1.0
5	**1a**	**2a**	**3c**	62	**6**[5a] (46)	1.8:1.0
6	**1a**		**3c**	99		
7	**1a**	**2b**	**3a**	10	**4b**[11] (16)	1.5:1.0
8	**1a**	**2c**	**3a**	15		
9	**1a**	**2d**	**3a**	22	**4d**[11] (19)	1.4:1.0
10	**1a**	**2e**	**3a**	10		

[a] Relative to the initial amount of indole. If calculations are done based on initial CHD, the yields are halved.

in 38% yield with an isomer distribution typical of a triplet-sensitized dimerization (*anti*-[2 + 2], *syn*-[2 + 2] and *exo*-[4 + 2] adducts obtained in a 3:1:1 ratio).[14] For comparison, irradiation during 1 h of BT in the presence of CHD, in the absence of indole, led to complete diene dimerization with the same isomer distribution (run 2, Table 1).[15]

Two substituted 2-benzoylthiophene derivatives **1b** and **1c** were also used as sensitizers, showing behavior similar to that of BT (runs 3 and 4 in Table 1). Besides, other cyclohexadienes instead of CHD were tested in the cross-cycloaddition with InH. No Diels–Alder adducts were obtained with α-terpinene **3b**, a 1,4-disubstituted cyclohexadiene, perhaps because of steric factors, and only aromatization of the diene was observed. However, the 2,5-disubstituted diene **3c** led to a higher yield of the Diels–Alder products compared to that of diene **3a** (run 5 in Table 1). The regioselectivity was similar to that previously reported in the cycloaddition of **3c** to the indole radical cation.[5] Also, substitution at the indole ring (as in **2b**–**2e**) showed a clear influence on the photochemically induced cross-cycloaddition with CHD. Thus, while **2b** and **2d** gave rise to the corresponding cycloadducts **4b** and **4d** in yields similar to that of **2a**, Diels–Alder products were detected only in trace amounts when using **2c** and **2e** as dienophiles (runs 7–10).

In the radical cation reaction between substituted indoles and CHD photocatalyzed by triarylpyrylium salts[5] the results have been explained through a mechanism involving initial attack at the C3 position of the indole radical cation, followed by ring closure to the C2 position.[16] Any substitution at C3 decreases the reaction yield as a result of steric repulsion, but the new bond is strong enough to compensate such an effect. However, when the ring closure step is hindered, the reaction becomes completely inhibited.

Our results in the 2-benzoylthiophene photocatalyzed reactions were not coincident with the Diels–Alder reaction through indole radical cations, since similar results were obtained with InH, 3-methylindole, and 5-methylindole. Moreover, in the case of 7-methylindole the process was completely inhibited, even if there is no steric repulsion to the cyclohexadiene attack at the 2,3-indolyl positions. This would be compatible with a significant steric hindrance in formation of the exciplex that must be attacked by CHD and is supported by DFT calculations (see below). Hence, time-resolved experiments and preliminary theoretical studies were performed to get some insight into the mechanism of the BT-catalyzed cycloaddition reaction.

Laser flash photolysis of dichloromethane solutions of BT in the presence of indoles **2a**–**2e** showed in all cases triplet quenching, with formation of BT ketyl/indolyl radical pairs (see Figure 1A and B for 5-methylindole and 7-methylindole, respectively). These radical pairs decayed mainly to the starting materials (as mentioned for InH),[10] since very low conversions were obtained after prolonged irradiation. Thus, they do not appear to play a key role in the cycloaddition process.

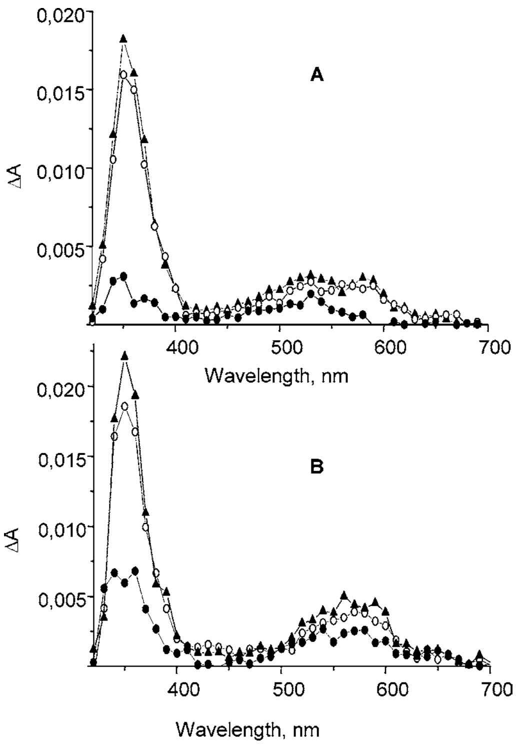


Figure 1. Transient absorption spectra recorded following laser excitation (355 nm) of dichloromethane solutions of BT (1.6 mM) in the presence of **2d** (16.0 mM, A) and **2e** (16.0 mM, B) under nitrogen (50 ns, ▲ and 1.5 μs, ○) and air (1.5 μs, ●) atmosphere.

---

(13) Tóth, M. *Chem. Phys.* **1980**, *46*, 437.

(14) Valentine, D.; Turro, N. J.; Hammond, G. S. *J. Am. Chem. Soc.* **1964**, *86*, 5202.

(15) The Stern–Volmer plot of the ratio of BT triplet lifetime in dichloromethane in the absence and presence of CHD afforded a quenching rate constant of $k_q = 4.7 \times 10^9$ M^{-1} s^{-1} (compared to $k_q = 2.0 \times 10^9$ M^{-1} s^{-1} for indole),[10] in agreement with the competition between the Diels–Alder reaction and the CHD dimerization.

(16) Saettel, N. J.; Wiest, O.; Singleton, D. A.; Meyer, M. P. *J. Am. Chem. Soc.* **2002**, *124*, 11552.

The nonlinear increase of the quenching rate constant with increasing quencher concentrations has been taken as an evidence for the involvement of exciplex intermediates.[9,17] Then, we determined such rate constants for the BT/InH pair. Indeed, a saturation behavior was evident at concentrations higher than 6.5 mM (Figure 2).

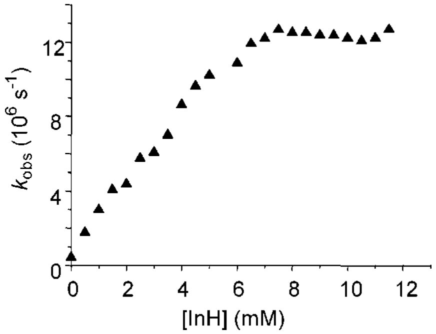


Figure 2. Saturation behavior of the observed first-order rate constants for the quenching of BT triplet by indole in dichloromethane.

On the other hand, preliminary DFT calculations (UB3LYP/6-31G* level)[18] were performed on the BT-photocatalyzed Diels−Alder reaction between indole and CHD. To estimate the catalytic effects of triplet BT on the cycloaddition reaction, two models were studied. The first one corresponds to the thermal Diels−Alder reaction between indole and CHD. The DFT calculations gave an asynchronous concerted mechanism where the C−C bond length at the C2 position of indole, 2.075 Å, was shorter than that at the C3 position, 2.373 Å. The potential energy barrier for this cycloaddition was 33.5 kcal/mol, although the process was exothermic by 10.7 kcal/mol. This large barrier should prevent the thermal Diels−Alder reaction between indole and CHD.

The second model studied was the ternary excited triplet state complex formed between CHD and the BT···HIn exciplex. The DFT calculations for this three-component Diels−Alder reaction at the triplet state were consistent with a stepwise mechanism initiated by the diene attack to the C3 carbon of indole. The length of the new C−C bond forming at the C3 position of indole was 2.246 Å, and the distance between the C2 carbon of indole and the end of the diene system was 4.094 Å. The geometry of the transition state is given in Figure 3. The potential energy barrier associated with the first step was ca. 1.5 kcal/mol, indicating that the Diels−Alder reaction for the triplet triplex would be largely accelerated compared to the thermal process. The intermediate resulting from complete formation of the σ bond (1.574 Å) at the C3 position was located 17.1 kcal/mol below the ternary triplet excited-state complex. Current work is being performed to achieve the complete characterization of all stationary points of this complex mechanism.

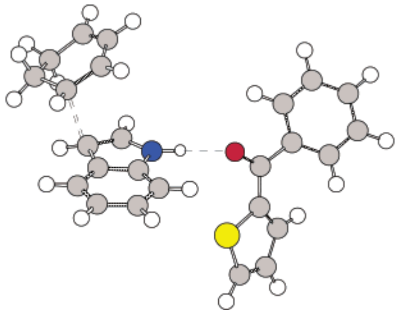


Figure 3. Transition structure associated with the attack of CHD to the C3 carbon of the BT···HIn exciplex.

In summary, experimental data indicate that the Diels−Alder cycloaddition between indoles and cyclohexadienes can be photocatalyzed by 2-benzoylthiophenes; the mechanism is new and involves formation of triplet triplexes by diene quenching of photosensitizer-dienophile exciplexes.

Acknowledgment. We thank the Spanish Government (Project BQU2002-00377) and the Generalitat Valenciana (Grupos 03/082) for generous support of this work.

OL048520C

---

(17) Hubig, S. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 1688.

(18) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.