

## Substituent Control of Excited State Reactivity: The Intramolecular Ortho Arene–Olefin Photocycloaddition

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The cycloaddition reactions of photoexcited benzene derivatives with olefins and other  $\pi$ -systems are among the most exciting recent developments in organic photochemistry.<sup>2</sup> While mechanistically intricate, these cycloadditions, in particular the meta variant, have proven to be an exceptionally powerful tool for the synthesis of complex molecules.<sup>3</sup> Paradigms developed from earlier investigations on the arene–olefin photocycloaddition have uniformly emphasized the degree of polarization between arene and olefin in the excited state as the critical factor in determining the mode (course) and the regio- and stereochemistry of these reactions.<sup>2</sup> The extent of charge transfer is, in turn, controlled by the nature of the substituents present on the reacting  $\pi$ -systems.<sup>2</sup> Cycloaddition between excited aryl groups and simple alkyl-substituted olefins generally leads to the formation of meta cycloadducts, while ortho photocycloaddition predominates from the singlet state when excited state charge transfer is energetically favorable; this is perhaps best exemplified by the selective ortho photocycloaddition between anisole and acrylonitrile.<sup>4</sup> Intramolecular ortho photocycloaddition from the triplet excited state of aryl ketone derivatives has also been extensively documented.<sup>5</sup> In accord with these charge transfer models, Wender has reported that irradiation of bichromophores having an anisole ring tethered to an alkyl-substituted olefin affords only products derived from meta arene olefin photocycloaddition.<sup>6</sup> We felt that the course of photocycloaddition in these anisole bichromophores could be diverted from meta to ortho by making charge transfer in the excited state energetically favorable, as would be expected in donor/acceptor bichromophores **1** and **2**.<sup>7</sup> Herein we report our efforts to more thoroughly describe the stereochemistry and regiochemistry of the intramolecular ortho photocycloaddition orig-

inating from the singlet excited state, as well as the reactivity of the resulting ortho cycloadducts.

This hypothesis is verified by experiment, as direct irradiation<sup>8</sup> of donor/acceptor bichromophore (*E*)-**1** affords no meta cycloadducts, but leads to the efficient formation of two photo-products **3** and **4** (58% and 14% yields, respectively, at 85% conversion, eq 1, Scheme 1).<sup>9</sup> The (*E*)-olefin geometry of **1** is preserved in the cis, anti adduct **3** (no products having H7 and H8 in a syn arrangement are formed).<sup>10</sup> Similarly, irradiation of (*E*)-**2** under identical conditions<sup>8</sup> affords the two diastereomeric adducts **5** and **6** in 50–55% isolated yield (in a 1.9:1 ratio) and tetraene **7** in 17% yield (at 85–90% conversion of **2**, eq 2).<sup>11</sup> The (*E*)-olefin geometry of **2** is also incorporated in each tricyclic adduct **5** and **6**. Again, no meta photocycloadducts are produced.<sup>10</sup> It is noteworthy that tetraenes **4** and **7**, which can be thought of as arising from formal metathesis of the aryl ring with the pendant olefin, have heretofore only been observed in intermolecular arene–olefin cycloadditions.<sup>4a,12</sup>

The formation of these adducts can be explained by invoking a cascade of pericyclic reactions initiated by a regio- and stereoselective intramolecular ortho arene–olefin photocycloaddition (Scheme 2). The regiochemistry of this cycloaddition is consistent with an excited state in which the substituents on the olefin and arene maximize stabilization of the developing charges, as only products resulting from cycloaddition across the 1 and 2 positions of the aryl ring (**9**) are produced.<sup>2</sup> Stereoelectronic considerations dictate that the olefin must approach the aryl ring in an exo facial manner, i.e., **8a** or **8b**, since an endo facial approach (**8c**) would result in the formation of an excessively strained cycloadduct.<sup>2e,f,13</sup> Cycloadducts **9** are labile and undergo facile thermal electrocyclic ring opening<sup>14</sup> to the bicyclo[6.3.0]undecatrienes **10**; photochemical disrotatory ring closure affords the tricyclics **3**, **5**, or **6** while the trienes **4** or **7** arise from electrocyclic ring opening and subsequent olefin isomerization.<sup>14</sup> It should be noted that in contrast to Wagner's

(7) Compounds **1** and **2** are both synthesized from 2-bromoanisole using the following series of reactions. (i) 1) Li(O), Et<sub>2</sub>O, 2,2-dimethylpent-4-en-1-yl, then NH<sub>3</sub> (72%);<sup>7a</sup> (ii) O<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>, then (CH<sub>3</sub>)<sub>2</sub>S (65%); (iii) (*i*-PrO)<sub>2</sub>POCH<sub>2</sub>CN, NaH, –78 to 0 °C (85%, 10.5:1 *E:Z* ratio of olefin isomers).<sup>7b</sup> **2**: (i) *n*-BuLi, Et<sub>2</sub>O, then 4-penten-1-yl (97%); (ii) *tert*-butyldimethylsilyl chloride (TBDMSCl), imidazole, dimethylformamide (79%); (iii) O<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>, then (CH<sub>3</sub>)<sub>2</sub>S (88%); (iv) (*i*-PrO)<sub>2</sub>POCH<sub>2</sub>CN, NaH, –78 to 0 °C (77%, 8.5:1 *E:Z* ratio of olefin isomers). The details of these syntheses will be disclosed in our full paper. (a) Hall, S. S.; McEnroe, F. J. *J. Org. Chem.* **1975**, *40*, 271 and references therein. (b) Dugger, R. W.; Heathcock, C. H. *Synth. Commun.* **1980**, *10*, 509.

(8) Typical photolysis conditions: Hanovia 450 W medium-pressure Hg lamp, Vycor filter, 20 °C, [1] or [2] = 5 mM in O<sub>2</sub>-free CH<sub>3</sub>CN. Acetonitrile has proven to be the most effective solvent for this reaction; photolysis in other solvents such as hexane, benzene, and *tert*-butyl alcohol led to lower yields and required longer reaction times. This solvent effect may also provide evidence for the importance of charge transfer in the initial ortho cycloaddition.<sup>2e,f</sup>

(9) The lower limit of our detection has been set at ca. 1–3% using HPLC analysis.

(10) The isolation of photoadducts **5**–**7** was facilitated by formation of their *p*-bromobenzoate derivatives. This was accomplished by submitting the crude photolysate to fluoridolysis (*n*-Bu<sub>4</sub>NF, THF, room temperature) followed by benzoylation (*p*-BrC<sub>6</sub>H<sub>4</sub>COCl, CH<sub>2</sub>Cl<sub>2</sub>, pyridine).

(11) The structure of **5c** was determined by single-crystal X-ray structure analysis. Oxidation of **5b** and **6b** to their corresponding enones afforded diastereomeric compounds, demonstrating that the stereochemistries of **5** and **6** differ at positions other than C-11. H7–H8 of **6** are in an anti orientation from the observation of an H11–H7 NOE enhancement and a lack thereof for H11–H8. Also, anti H7–H8 coupling constants generated with Macromodel v. 4.5 under MM3 conditions are in agreement with the NMR data for **5** and **6** (calculated to be 1.0 Hz for the singlet seen in **5** and 12.6 Hz for the observed 12.2 Hz doublet in **6**; coupling constants generated if H7–H8 were in the two possible syn configurations were 2.9 and 5.7 Hz). C-3–C-6 must be syn fused; therefore, it follows that the substituents C-3–C-6 and C-7–C-8 must be oriented as drawn for **6**. The assignment of H11 for **6** is based on a NOE for H7–H11. A similar enhancement in **5** is not observed.

(12) (a) Atkinson, J. G.; Ayer, D. E.; Büchi, G.; Robb, E. W. *J. Am. Chem. Soc.* **1963**, *85*, 2257. (b) Kaupp, G.; Jostkleigrewe, E. *Angew. Chem.* **1976**, *88*, 812. Each tetraene **4** and **7** also contained an isomeric tetraene, ca. 8–10%; the configuration of this compound has not yet been identified.

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(2) For recent reviews on this expanding topic, see: (a) Morrison, H. *Acc. Chem. Res.* **1979**, *12*, 383. (b) Wender, P. A.; von Geldern, T. W. *Photochemistry in Organic Synthesis*; Coyle, J. D., Ed.; Special Publication No. 57, Royal Society of Chemistry: London, 1986; p 226. (c) Wender, P. A. *Selectivity—A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag-Chemie: Heidelberg, 1984; p 335. (d) Mattay, J. *Angew. Chem.* **1987**, *99*, 849. (e) Wender, P. A.; Siggel, L.; Nuss, J. M. *Org. Photochem.* **1989**, *10*, 487. (f) Wender, P. A.; Siggel, L.; Nuss, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: London, 1991; Vol. 5, p 335. (g) Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615.

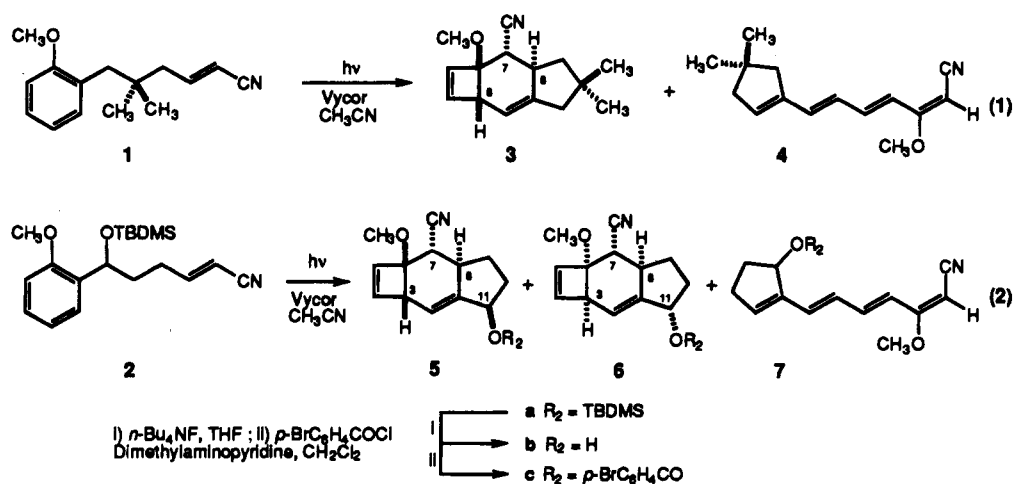
(3) For a discussion of molecular complexity as it applies to the synthesis of complex molecules, see: (a) Bertz, S. H. *J. Am. Chem. Soc.* **1981**, *103*, 3589. (b) Wender, P. A.; von Geldern, T. W.; Levine, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 4858. For a comprehensive discussion of this aspect of the arene–olefin photocycloaddition, see ref 2e,f.

(4) Gilbert, A.; Yianni, P. *Tetrahedron* **1981**, *37*, 3275 and references therein.

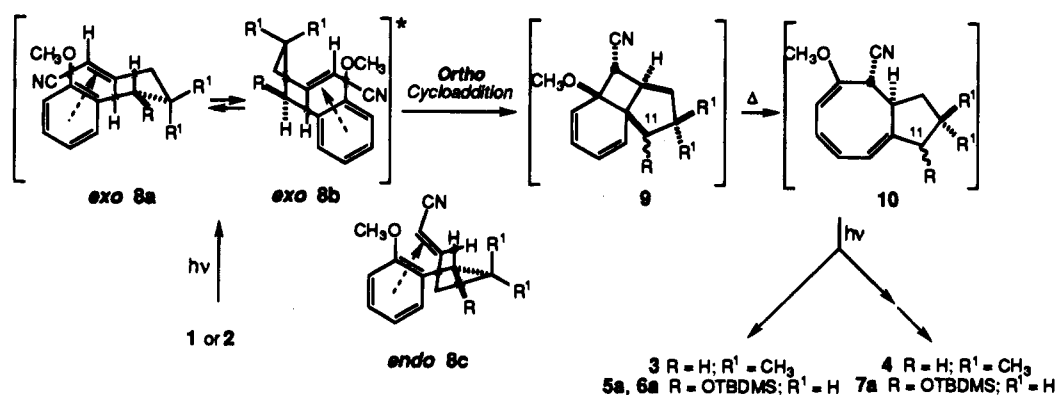
(5) (a) Wagner, P. J.; Sakamoto, M.; Madkour, A. E. *J. Am. Chem. Soc.* **1992**, *114*, 7298. (b) Wagner, P. J.; Nahm, K. *J. Am. Chem. Soc.* **1987**, *109*, 4404, 6528. (c) Wagner, P. J.; Sakamoto, M. *J. Am. Chem. Soc.* **1989**, *111*, 1145, 8723. (d) Wagner, P. J.; Cheng, K.-L. *Tetrahedron Lett.* **1993**, 907. (e) Wagner, P. J.; Alehashem, H. *Tetrahedron Lett.* **1993**, 911. (f) Wagner, P. J.; McMahon, K. *J. Am. Chem. Soc.* **1994**, *116*, 10827. (g) Wagner, P. J.; Cheng, K.-L. *J. Am. Chem. Soc.* **1994**, *116*, 7945. (h) Al-Qaradawi, S. Y.; Cosstick, K. B.; Gilbert, A. *J. Chem. Soc., Perkin Trans J* **1992**, 1145.

(6) Wender, P. A.; Fisher, K. J. *Tetrahedron Lett.* **1987**, 1857.

## Scheme 1



## Scheme 2



results in the aryl ketone triplet photocycloadditions, where both the initial photoadduct and its thermal opening to a very stable cyclooctatriene were isolable,<sup>5a,b,d,f</sup> intermediates **9** and **10** are not isolable.<sup>15</sup> The tricyclic photoproducts **3**, **5**, and **6** do not open to cyclooctatrienes upon extended thermolysis; the tetraenes **4** and **7** are also thermally stable.

The stereoselective incorporation of the (*E*)-olefin geometry in the tricyclic adducts during this reaction sequence provides supporting evidence for a process initiating from the first excited singlet state ( $S_1$ ) of the anisole chromophore; this high level of stereoselectivity has also been observed in intramolecular meta photocycloadditions arising from the singlet state.<sup>2e,f</sup> The modest benzylic diastereoselection (1.9:1) observed in the photolysis of **2** stands in contrast to related meta cycloadditions, which typically exhibit ca. 5-fold higher levels of benzylic stereoselection.<sup>2e,f,5</sup> This attenuation may reflect the small energetic difference between two reactive exo conformers **8a** and **8b**, each having the benzylic substituent in a favorable pseudoequatorial orientation; these then afford diastereomeric ortho photoadducts **9** (epimeric at C-11). Ring opening of these C-11 epimers and subsequent photochemical ring closure yields

**5** and **6**, respectively. It is interesting to note that it appears as though each diastereomeric ortho photocycloadduct (deriving from exo conformers **8a** and **8b**, respectively) leads to a different "torquoselectivity" in the final disrotatory electrocycloaddition (**10** to **5** and **6**).<sup>14,16</sup> The factors controlling the stereochemistry of these reactions continue to be investigated.

In conclusion, these studies have demonstrated the profound influence of substituents on the course of the arene-olefin photocycloaddition and have begun to address several critical aspects of the ortho variant of this reaction, including the preferred mode and the regio- and stereochemical pathways of donor/acceptor bichromophores. The cascade of reactions initiated by the photocycloaddition leads to a striking increase in the molecular complexity of these systems, producing highly functionalized adducts which should have considerable potential for further elaboration. Further investigations in this area will be reported in due course.

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**Supplementary Material Available:** Complete spectral and analytical data for compounds **1-4**, **5c**, **6c**, and **7c** and complete X-ray crystallographic data for **5c** (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

(13) This aspect of the intramolecular meta arene-olefin photocycloaddition has been discussed by Wender: Wender, P. A.; Howbert, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 688. See also refs 2e,f.

(14) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980.

(15) Photolysis of **1** or **2** under conditions in ref 8 at  $-20^\circ\text{C}$  yielded only photoproducts **3** and **4** and **5**, **6**, and **7**, respectively. No amounts of **9** or **10** were detected.

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