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Dipole-mediated regioselectivity in the [2+2]-photocycloaddition of double bonds to triplet benzenes

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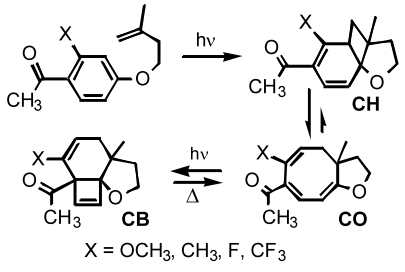
Abstract—The regioselectivity of the intramolecular [2+2] photocycloaddition of 2-substituted 4-butenoxybenzaldehydes and 4-butenoxybenzonitriles and of two 4-butenoxybenzocycloalkanones has been investigated. *para*-(3-Buten-1-oxy)benzaldehydes with *ortho* methyl and trifluoromethyl substituents undergo regioselective *syn* cycloaddition, while 4-butenoxy tetralone, chromanone, and 2-methoxybenzaldehyde undergo mainly *anti* cycloaddition. *ortho* Substituted *p*-butenoxybenzonitriles and *o*-fluoro-*p*-butenoxybenzaldehyde produce both regioisomers. These results provide more evidence that the C=O dipole largely determines selectivity, something the cyano group's alignment prevents. Computations augment the conclusion that the observed regioselectivity results primarily from interactions between the intrinsic molecular dipole of the triplet state and the charge transfer induced dipole in the exciplex state.

Over a decade ago we reported that remote double bonds undergo intramolecular [2+2] photocycloaddition to the π,π* triplet state of acylbenzenes.[1] The bicyclo[4.2]octa-2,4-diene component of the initial tricyclic photoproducts CH undergoes rapid thermal equilibration with a cycloöctatriene structure to form bicycle CO, one diene unit of which then undergoes photocyclization to a cyclobutene ring to generate another tricyclic product CB.[2] A full account of this process has been reviewed recently.[3] Both *meta*- and *ortho*-substituted *para*-alkenoxyacetophenones exhibit very high regioselectivity, cycloaddition generally occurring only *syn* to the substituent, as shown below for *ortho* substituents. This paper addresses that selectivity.



In the case of *meta* substituents, both electronic and steric factors affect selectivity, with the latter dominating.[4] The electronic factor affects both kinetics and selectivity: the rate constant for cycloaddition is 20 times faster for *m*-cyano than for *m*-methoxy; and only alkoxy groups are strong enough electron donors to overcome the steric preference for *syn* addition. This electronic effect offers evidence for an exciplex precursor to the actual addition, with charge-transfer from the double bond to the more electron deficient side of the benzene ring being favored.

In the case of *ortho* substituents, the orientation of the carbonyl appeared to determine selectivity.[5] Inductive effects like those for *meta* substitution seem unlikely, given the identical selectivity for both electron donors and acceptors. Substituents *ortho* to the acyl group are too far from the reaction center to have a direct steric effect on cycloaddition; but steric factors do favor the conformer with the acetyl carbonyl pointed toward most *ortho* substituents. Only with fluorine, the smallest substituent studied, are both regioisomers formed. Moreover, 4-butenoxyindanone, whose carbonyl points away from the '*ortho*'-methylene group, undergoes only *anti*-addition.[5] In order to gather more information about whether the carbonyl orientation affects selectivity by its dipole moment, we have studied the photoproducts from 2-substituted 4-butenoxy benzaldehydes and benzonitriles. Our strategy assumed that the formyl group is more likely than acetyl to exist in both *syn* and *anti* rotamers, while the linear cyano group could not of itself induce any regio-preference.

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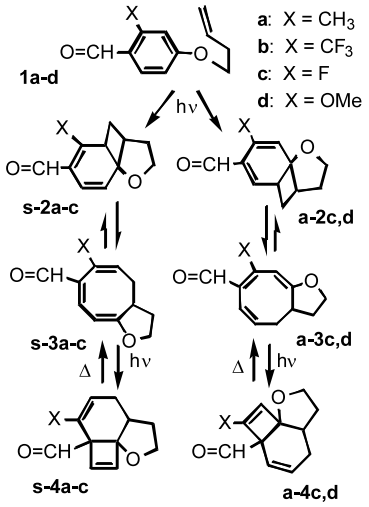
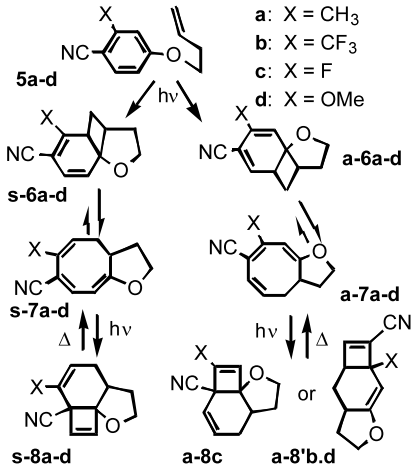
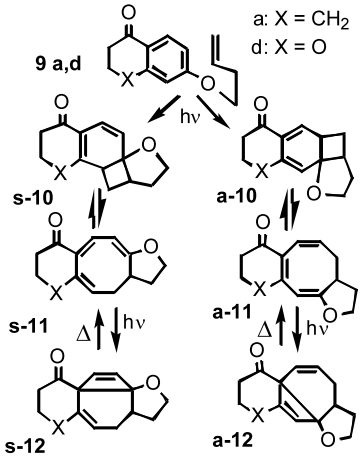


Scheme 1.



Scheme 2.



Scheme 3.

Schemes 1–3 indicate all of the compounds that we have studied[†] and the isomeric photoproducts produced by UV irradiation of de-aerated acetonitrile solutions ~0.02 M in reactant.[‡] Product identification was carried out from ^{1}H NMR spectra of reaction solutions and by HPLC separation of products from preparative scale irradiations. As noted earlier,[3] different *ortho* (as well as *meta*) substituents strongly affect CH ⇌ CO ⇌ CB equilibria; so regioselectivity was determined from the NMR spectra of different products for different substituents X. Thus **s-4** is differentiated from **a-4** by the two coupled doublets for the cyclobutene vinyl protons; **a-2** or **s-3** from **s-2** or **a-3**, by an enone vinyl proton signal around 7 ppm. For benzaldehydes **1a**–**c**, the predominant photoproducts resulted from *syn* addition, whereas all four benzonitriles **5** gave both *syn* and *anti* addition products, as determined by direct NMR analysis. Benzaldehyde **1d** and the cyclic ketones **9a** and **9d** underwent *anti* addition with over 90% selectivity.

Aldehydes **1a** and **1b** formed **s-4a** and **s-4b** that revert thermally to **s-3a** and **s-3b**; **1c** provided a mixture of **s-4c**, **s-3c** and **a-3c**[§] in a 1.7:1:1 ratio; **1d** produced **a-2d**,[¶] very little of which equilibrates with **a-3d**, as observed for the photoproducts of 3-methoxy-4-butenoxyacetophenone.[4]

Product yields were low in all cases due to the high photoreactivity of aldehydes, especially for **1a** where the methyl group is subject to hydrogen abstraction. It is possible that some *anti* addition products were less stable than the *syn* products identified and isolated; but the equal formation of **s-3c** and **a-3c** suggests that intrinsic skeletal instability is an unlikely cause for the lack of any **a-3a**, **s-3b**, or **s-4d** products.

[†] Compounds **2**–**6**, and **8** were prepared by bromination of appropriately substituted phenols followed by standard van Braun cyanization. Reduction using DIBAH followed for **2**, **3** and **4**. Compounds **1** and **7** were prepared by Fries rearrangements of *meta*-substituted phenyl acetates.

[‡] Reactants were irradiated with the 313 nm output of a medium pressure mercury arc lamp or with the '300 nm' lamps in a Rayonet reactor.

[§] **3c**: ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.86 (d quar, J=13.19, 6.59 Hz, 1H9), 2.20 (d quar, J=14.28, 7.14 Hz, 1H9′), 2.31 (dtd, J=15.93, 9.34, 7.14 Hz, 1H7), 2.53 (d quar, J=15.9, 3.3 Hz, 1H7), 3.05 (m, 1H8), 4.23 (dt, J=8.79, 7.14 Hz, 1H10), 4.33 (dt, J=8.79, 6.59 Hz, 1H10), 5.57 (d, J=6.59 Hz, 1H2), 5.76 (dt, J=23.07, 6.59 Hz, 1H6), 7.08 (d, J=7.14 Hz, 1H3), 9.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 27.99, 31.23, 41.38, 70.02, 96.37, 111.36, 128.35, 148.63, 154.99, 173.19, 191.23.

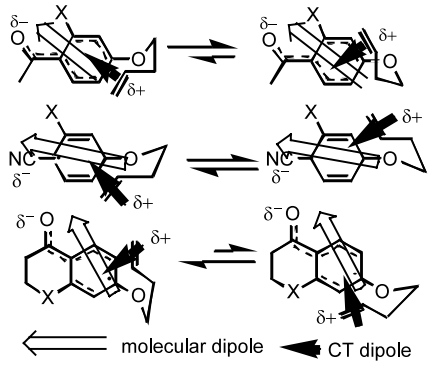
3c′: ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.87 (dddd, J=12.08, 10.99, 7.69 and 6.59 Hz, 1H9), 2.25 (dddd, J=12.08, 11.54, 8.24, 7.69 Hz, 1H9′), 2.43 (dd, J=11.74, 5.49 Hz, 2H7), 3.32 (m, 1H8), 4.35 (ddd, J=8.79, 8.24, 7.69 Hz, 2H10), 5.40 (d, J=10.44 Hz, 1H2), 5.89 (dt, J=12.64, 5.49 Hz, 1H6) and 6.15 (dd, J=12.64, 4.4 Hz, 1H5), 10.09 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 19.40, 33.65, 67.09, 73.27, 112.05, 116.5 (d), 127.89, 134.45, 137.70, 160.50 (d), 206.60.

[¶] **4b′**: ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.96 (tdd, J=16.11, 7.81, 7.32 Hz, 2H9), 2.17 (dddd, J=17.1, 5.37, 2.44, 1.95 Hz, 1H7), 2.42 (m, H8), 2.70 (dd, J=17.09, 2.44 Hz, 1H7), 3.37 (br d, J=4.9, 1H6), 3.64 (s, Me) 3.82 (m, 2H10), 4.66 (s, H2), 6.78 (dd, J=5.37, 2.93 Hz, 1H5), 9.47 (s); ^{13}C NMR ($CDCl_3$, 300 MHz, δ): 21.27, 28.96, 36.92, 52.02, 56.96, 65.48, 82.40, 96.81, 139.65, 147.63, 156.41, 193.49.

The benzonitriles were irradiated in acetonitrile containing acetone as a sensitizer to enhance formation of triplet states.[6] Compound **5a** provided **a-7a** and **a-8a** in a 3:1 ratio; **5b** produced **a-7b**, **s-8b**, and **a-8′b** in a 10:1:1 ratio; and **5c** generated a mixture of **s-8c** and **a-8c** in a 1:2 ratio. As in earlier studies of benzonitriles,[6,7] the cycloöctatriene products **7** tend to photocyclize to both **8** and **8′** cyclobutene structures; **5d** afforded **s-8d** and **a-8d** in a 1:1 ratio.‖

Tetralone **9a** produced **a-12a**, **a-11a**, and **s-10a** in a 10:2:1 ratio, showing *anti* selectivity, opposite that for *o*-methyl-*p*-butenoxyacetophenone and **1a**. Chromanone **9d**, unlike *o*-methoxy-*p*-butenoxyacetophenone, also showed *anti* selectivity, forming **a-11d**** and **s-12d** in a 1:10 ratio.

These results support our earlier speculation that the high regioselectivity for *o*-substituted *p*-butenoxyphenyl ketones is determined mainly by the direction of the dipole associated with the carbonyl. That the nitriles undergo cycloaddition both *syn* and *anti* to all four *ortho* substituents is in accord with the alignment of the cyano group's dipole being the same for both directions of addition. Ketones **9** and **10** both undergo predominantly *anti* addition, like the indanone studied earlier. We believe that the dipole moment induced during charge transfer from the double bond to the benzene ring interacts with the molecular dipole moment, which is dominated by the cyano or carbonyl group and modified by *ortho* substituents. As Scheme 4 shows, the favored mode of addition should be the one in which the charge transfer dipole is perpendicular rather than parallel to the molecular dipole. We had thought that the benzaldehydes would undergo more *anti* addition, based on computations indicating that the favored geometry of the formyl group in both ground and triplet states has the carbonyl pointing away from *ortho* substituents. However, ab initio calculations of the molecular dipole moment of triplet states indicate that the most electron withdrawing *ortho* substituents swing the molecular dipole so as to favor *syn* addition. We shall pursue this intriguing phenomenon with further computational and experimental studies, especially of substituent effects on product interconversion.



Scheme 4.

Acknowledgements

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‖ **8d**: ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.85 (ddd, J=9.89, 9.34, 7.14 Hz, 1H6), 2.06 (ddd, J=14.28, 7.14, 3.85 Hz, 1H4), 2.34 (ddd, J=9.89, 6.59, 3.30 Hz, 1H6), 2.49 (m, 1H5), 2.53 (ddd, J=15.38, 8.79, 3.85 Hz, 1H4), 4.02 (ddd, J=8.79, 3.85 Hz, 1H7), 4.19 (ddd, J=8.79, 8.24, 7.69 Hz, 1H7), 6.22 (d, J=2.75 Hz, 1H11), 6.31 (d, J=2.75 Hz, 1H10) and 6.51 (m, 1H3).

8e′: ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.32 (m, J=11.54, 7.69 Hz, 1H6), 1.73 (dddd, J=11.54, 8.79, 7.69, 2.2 Hz, 1H6), 2.22 (ddd, J=15.93, 6.59, 1.65 Hz, 1H8), 2.27 (ddd, J=15.93, 7.14, 1.65 Hz, 1H8), 2.33 (m, H7), 3.35 (dd, J=5.49, 1.65 Hz, 1H9), 4.03 (ddd, J=8.79, 8.24, 7.14 Hz, 1H5), 4.30 (ddd, J=8.79, 8.24 Hz, 1H5), 4.93 (d, H=3 Hz, 1H2), 6.94 (br s, H10).

** **10h′**: ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.84 (ddt, J=12.40, 6.26, 5.95 Hz, 1H13), 2.24 (dddd, J=12.40, 6.59, 6.22, 4.3 Hz, 1H13), 2.38 (dtd, J=10.44, 6.51, 4.42 Hz, 1H11), 2.42 (td, J=15.31, 3.85 Hz, 1H6), 2.51 (m, J=10.44, 1H11), 2.77 (td, J=15.31, 3.2 Hz, 1H6), 3.37 (m, 1H12), 4.35 (t, J=7.8 Hz, 2H5), 4.38 (td, J=8.54 , 3.30 Hz, 1H14), 4.47 (td, J=8.54, 6.59 Hz, 1H14), 5.39 (s, 1H2), 5.83 (dt, J=12.5, 4.5 Hz, 1H10) and 6.22 (br d, J=12.5 Hz, 1H9).