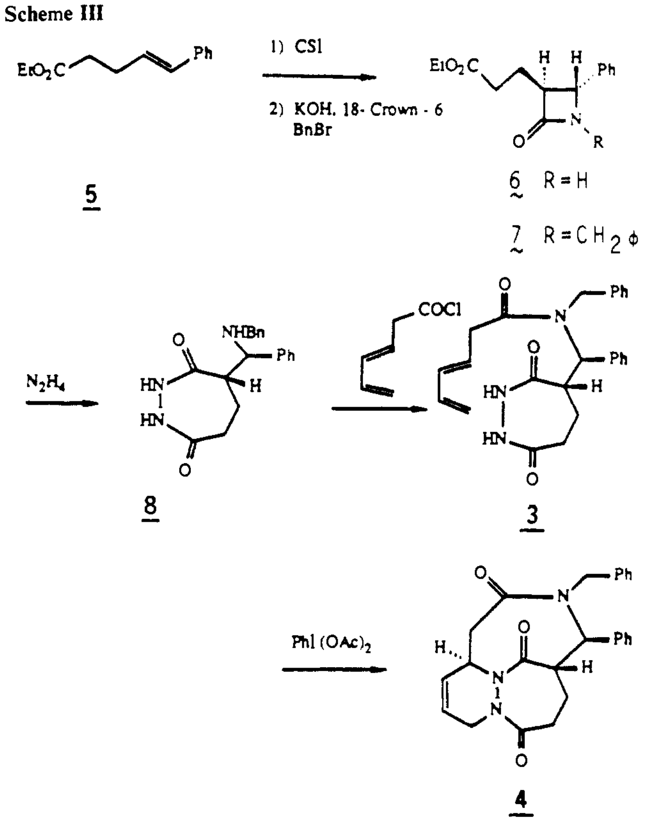
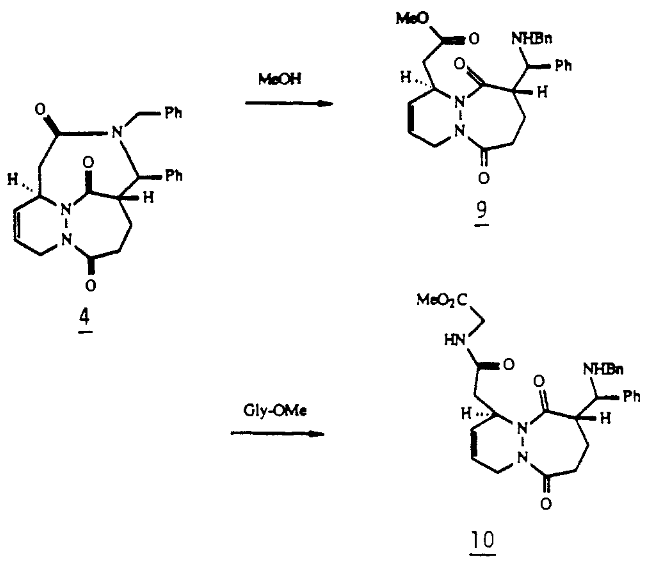
Scheme III



Yamazaki protocol[10] affords **7** in 79% yield after chromatography. Hydrazine treatment (refluxing methanol, 24 h) generates diacylhydrazide **8** in 84% yield.[11] Acylation of **8** with 3,5-hexadienoyl chloride[12] provides the penultimate intermediate **3**. Oxidation with iodosobenzene diacetate[13] generates the requisite dienophile **2**, which undergoes an extremely facile (15 min, 80 °C) exo cycloaddition to afford **4** in 97% yield.[14] Upon methanolysis (room temperature MeOH, pyridine), amino ester **9** is generated quantitatively[15] (see Scheme IV). Significantly, reaction of **4** with glycine methyl ester in methylene chloride at ambient temperature provides hybrid mimetic **10**.[16]

This intramolecular cycloaddition strategy provides rapid entry into β-turn mimetic systems of type **1**. Extension and utilization of this approach to prepare biologically relevant mimetics and mimetic hybrids are in progress and will be reported in due course.

Scheme IV



Acknowledgment. We acknowledge the generous financial support of the Camille and Henry Dreyfus Foundation (Distinguished Young Faculty Fellowship), Searle Scholars Program/The Chicago Community Trust, the NSF (Presidential Young Investigator Award), Abbott, Hoffmann-La Roche, Monsanto, Procter and Gamble, Schering and Syntex for matching funds, the American Cancer Society (Junior Faculty Fellowship), and Dr. Michael Johnson (UIC Department of Medicinal Chemistry) for many stimulating discussions. Additionally we thank the NSF (Grant no. 2-5-28317) for funds for purchase of a 400 MHz NMR spectrometer.

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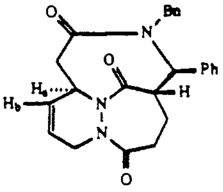
(10) Hirai, Y.; Kamide, I.; Yamazuki, T. *Heterocycles* **1981**, *15*, 1101.

(11) This reaction proceeds via initial formation of the β-lactam acylhydrazide. This is critical in that the cyclization of succinic esters to diacylhydrazides is quite problematic (see, for example: Miller, D. M.; White, R. W. *Can. J. Chem.* **1956**, *34*, 1510). In this instance the β-lactam presumably acts as an activated acyl group and lowers the entropic factors which disfavor the seven-membered ring closure.

(12) Martin, S. F.; Tu, C.-Y.; Chou, T.-S. *J. Am. Chem. Soc.* **1980**, *102*, 5274.

(13) Moriarty, R. M.; Prakash, R. M. I.; Penmasta, R. *Synth. Commun.* **1987**, 409.

(14) Stereochemical assignment was made on the basis of the less than 2 Hz coupling constant between protons H_a and H_b and comparison with molecular modeling.



(15) The extreme mildness of the methanolysis reaction highlights the strain and reactivity of the tricyclic system of lactam **4**.

(16) We define mimetic hybrids as synthetic units coupled to oligopeptides.

The π-Complex Benzene-Ethylene Cation Radical

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It has been known for some time that under suitable conditions planar conjugated hydrocarbons M upon ionization in solution form π-complexes $(M)_2^{\bullet+}$ consisting of two such species carrying a single charge.[1] Apart from coulombic and dispersive attractions such dimer cations are bound by substantial covalent or resonance contributions ΔH_{res} arising mainly from the interaction between the two HOMOs of M and $M^{\bullet+}$ as depicted in Figure 1a. Spectroscopically, $(M)_2^{\bullet+}$ distinguish themselves from the monomeric constituents by an additional intense absorption in the near-infrared spectral range which is attributed to so called "charge resonance" (CR) transitions of energy E_{CR}.[2] If follows from the qualitative MO diagram in Figure 1a that the energy of these transitions E_{CR} is independent of ϵ_{HOMO} of M involved and should hence be a direct measure of ΔH_{res} between M and $M^{\bullet+}$. Indeed, both E_{CR}[3] and ΔH_{res}[4] are found to decrease slightly with the size

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(1) Badger, B.; Brocklehurst, B. *Trans. Faraday Soc.* **1969**, *65*, 2576, 2582, 2588.

(2) Badger, B.; Brocklehurst, B. *Nature (London)* **1968**, *219*, 263. Badger, B.; Brocklehurst, B. *Trans. Faraday Soc.* **1970**, *66*, 2939.

(3) Kira, A.; Imamura, M. *J. Phys. Chem.* **1979**, *83*, 2267.

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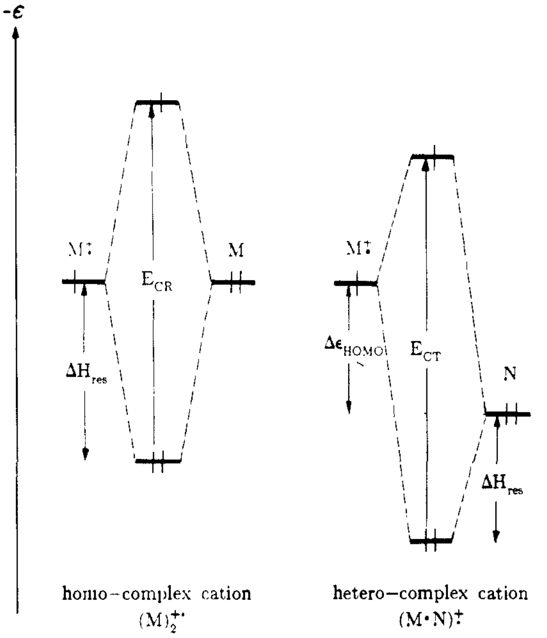


Figure 1. Electronic structure of (a) homo- and (b) hetero-complex cations.

of M in a series of polycyclic aromatic hydrocarbons with widely varying ionization energies ($-\epsilon_{HOMO}$).[5]

On the other hand such ionized complexes can also be formed between two *different* planar π-systems M and N. Such species $(M\cdot N)^{\cdot +}$ have been observed by mass spectrometric techniques and it was found that their dissociation energy ΔH_D is always smaller than that of the homocomplex cations $(M)_2^{\cdot +}$ or $(N)_2^{\cdot +}$, respectively.[4] An explanation for this is that ΔH_{res} (and hence its contribution to ΔH_D) decreases with increasing $\Delta\epsilon_{HOMO}$ as depicted in Figure 1b. It is probably because of this thermodynamic bias for homocomplex cations that their hetero analogues are difficult to prepare in condensed phase and to study by optical spectroscopy although they should show absorptions of a similar type as that encountered in dimer cations. Since the corresponding electronic transitions entail a partial charge *transfer* they should be termed charge transfer (CT) rather than charge resonance (CR) absorptions.[6]

In the course of our work on the spectroscopy and photochemistry of polyene cations and their (poly)cyclic valence isomers[7] we recently studied the photochemistry of the $C_8H_{10}^{\cdot +}$ valence isomers, bicyclo[4.2.0]octa-2,4-diene cation radical (BCO$^{\cdot +}$) and 1,3,5-cyclooctatriene cation radical (COT$^{\cdot +}$). In argon matrices both species show complex spectra indicating partial rearrangement to 1,3,5,7-octatetraene cation radical (OT$^{\cdot +}$) in different

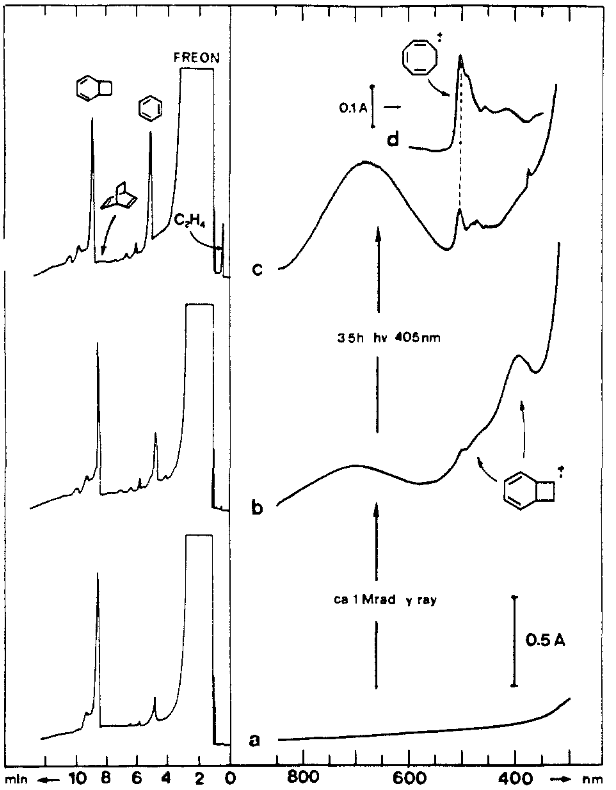
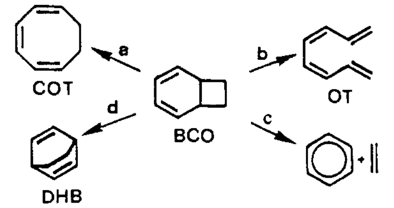


Figure 2. Right-hand side: Electronic absorption spectra of 3.5 × 10^{-2} M BCO in FM[8b] at 77 K (a) before and (b) after ≈1 Mrad γ-irradiation. The band at 400 nm and the shoulder at 490 nm in spectrum b are due to BCO$^{\cdot +}$.[8a] (c) Same sample after 3.5 h of photolysis at 405 nm. (d) Spectrum of 5 × 10^{-2} M COT after ionization (note different scale, all spectra taken 1-mm cells). Left-hand side: GC traces of the samples showing spectra a–c after thawing.[15]

Scheme I



conformations upon ionization.[7d] This rearrangement can be carried to completion by visible irradiation in both cases. However, in a frozen Freon mixture (FM) where essentially pure spectra of the primary cations are obtained after γ-irradiation,[8] we were surprised to find that BCO$^{\cdot +}$ shows a very different photochemistry (Figure 2) leading to a species with an intense broad absorption (λ_{max} = 680 nm) reminiscent of—but at shorter wavelength than—the above mentioned $(M)_2^{\cdot +}$ CR transitions. Since the BCO concentrations were rather low and the intensity of the 680-nm band did not change upon slow annealing of the sample[9] $(BCO)_2^{\cdot +}$ could not be the species responsible for this band and another interpretation was called for.

A choice of possible rearrangements of BCO$^{\cdot +}$ is depicted in Scheme I. It includes (a) electrocyclic ring opening to cyclooctatriene (COT),[10] [2π + 2π] cycloreversions[11] to (b) octatetraene

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(4) Meot-Ner M. *J. Phys. Chem.* **1980**, *84*, 2724 and references cited therein. See also: Stone, J. A.; Lin, M. S. *Can. J. Chem.* **1980**, *58*, 1666.

(5) To our best knowledge, a direct comparison between the two related quantities, ΔH_{res} and E_{CR}, has never been attempted and is indeed fraught with certain problems: First, E_{CR} are usually measured in condensed phase and can therefore not be compared directly to the gas-phase ΔH_{res}. Secondly, ΔH_{res} are not observable quantities but must be deduced from $(M)_2^{\cdot +}$ dissociation energies ΔH_D by subtracting the electrostatic contributions that are obtained from ΔH_D of related complexes $(MH\cdot M)^+$ where ΔH_{res} is assumed to be zero. In view of all this, it is not surprising that (although the trends are similar) ΔH_{res} and $0.5E_{CR}$ differ substantially, the latter being 4–10 times larger.

(6) There is a report in the literature where the formation of a heterocomplex cation between pyrene and naphthalene was postulated (Kira, A.; Nakamura, T.; Imamaura, M. *Chem. Phys. Lett.* **1978**, *54*, 582). However, its CT absorption could not be detected, presumably because is was masked by $(M)_2^{\cdot +}$ CR bands.

(7) Bally, T.; Nitsche, S.; Roth, K.; Haselbach, E. *J. Am. Chem. Soc.* **1984**, *106*, 3927. (b) Bally, T.; Nitsche, S.; Roth, K.; Haselbach, E. *J. Phys. Chem.* **1985**, *89*, 2518. (c) Bally, T.; Nitsche, S.; Roth, K.; *J. Chem. Phys.* **1986**, *84*, 2577. (d) Bally, T.; Haselbach, E.; Nitsche, S.; Roth, K. *Tetrahedron* **1986**, *42*, 6325.

(8) (a) Bally, T.; Nitsche, S.; Roth, K.; Straub, R., manuscript in preparation. (b) We used a 1:1 mixture of $CF_2Br–CF_2Br$ (F114) and $CFCl_3$ (F11) as proposed originally by C. Sandorfy. See: Grimison, A.; Simpson, G. A. *J. Phys. Chem.* **1968**, *72*, 1776. Shida, T.; Iwata, S. *J. Am. Chem. Soc.* **1973**, *95*, 3473.

(9) Dimer cations are observed either in >10^{-2} M solutions[1] or in less concentrated solutions upon controlled annealing of the frozen glass.[3]

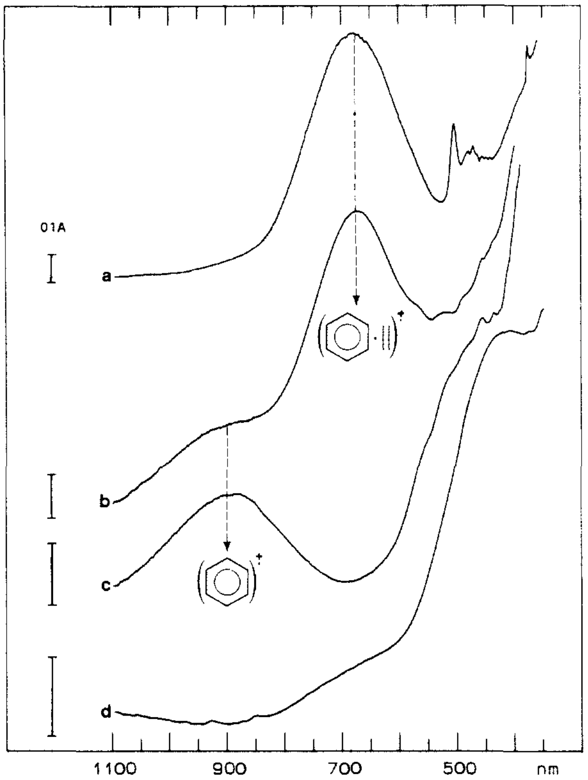

Figure 3. (a) Spectrum of Figure 1c redrawn; (b) 5 × 10^{-2} M frozen solution of benzene in FM[8b] saturated with ethylene (≈0.2 M) after ≈0.5 Mrad γ-irradiation; (c) same as part b *without* ethylene; (d) frozen FM saturated with ethylene after ≈0.5 Mrad γ-irradiation (all spectra taken in 1-mm cells).

(OT) or (c) benzene and ethylene, and (d) [1,3] sigmatropic shift to the [2.2.2] isomer, dihydrobarrelene (DHB).[12]

With respect to the present experiment we note immediately that reaction b does not occur because the intense sharp peaks of $OT^{\bullet+}$ between 500 and 450 nm are absent.[13] On the other hand, the new peak at λ_{max} = 505 nm indicates the presence of a small amount of $COT^{\bullet+}$, i.e., a minor participation[14] of path a. In order to assess possible contributions from reactions c and d to the new 680-nm band, BCO samples were subjected to GC analysis before and after ionization and subsequent photolysis, respectively.[15] The results of these analyses which are shown on the left-hand side of Figure 2 show clearly that photolysis of $BCO^{\bullet+}$ is accompanied by the rise of GC peaks corresponding to benzene and ethylene[16] while no trace of DHB can be detected in the same samples.[17]

In order to ascertain that the cleavage to benzene and ethylene occurs indeed as a result of the photolysis of $BCO^{\bullet+}$ (and not during sample warmup) an independent preparation of a benzene–ethylene cation radical ($(BZ{\cdot}ET)^{\bullet+}$) complex was attempted. Thus, matrix-isolated samples of BCO[19] were exhaustively photolyzed prior to ionization in order to pre-form benzene–ethylene complexes[11] but unfortunately, only $OT^{\bullet+}$ was observed after ionization of such samples, presumably because the other primary photoproduct, OT (I_1 = 7.8 eV), is at a ≈1.5 eV advantage in trapping holes if compared to benzene (I_1 = 9.25 eV). On the other hand, γ-irradiation of frozen FM solutions of benzene (5 × 10^{-2} M) saturated with ethylene (≈0.2 M) resulted in the appearance of the very same 680-nm band (Figure 3b) together with that of benzene dimer cation radical ($(BZ)_2^{\bullet+}$) at 920 nm[1]. Note that the 680-nm band is absent in ionized frozen FM solution containing only benzene or ethylene, respectively (Figure 3c,d).[20]

The combined evidence obtained from the above experiments leads us to propose that the intense absorption at λ_{max} = 680 nm is caused by a CT absorption of the novel heterocomplex $(BZ{\cdot}ET)^{\bullet+}$.[21] The diagrams in Figure 1 call for a semiquantitative rationalization of this spectral manifestation. Solution of an eigenvalue problem with the gas-phase ionization energies of the two constituent molecules (benzene 9.25 eV, ethylene 10.5 eV) as basis energies and an off-diagonal interaction term similar to that in $(BZ)_2^{\bullet+}$, i.e., $0.5E_{CR}$ = 0.67 eV,[22] yields two states separated by 1.83 eV (corresponding to 675 nm). It is gratifying to note the excellent agreement with experiment obtained with this rather crude model.

Acknowledgment. This work is part of project No. 2.044-0.86 of the Schweizerischer Nationalfonds zur Förderung der Wissenschaften. Helpful comments by Prof Shida (Kyoto University)[12,21] are gratefully acknowledged.

Registry No. $BCO^{\bullet+}$, 112221-03-1; benzene, 71-43-2; ethylene, 74-85-1.

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(10) Note that in neutral BCO this is not a primary photochemical reaction because it is oribtal symmetry forbidden (see also ref 11). However, just as in the neutral, $COT^{\bullet+}$ may arise as a secondary (photochemical or thermal) product, i.e., by recyclization of cis–cis $OT^{\bullet+}$ (formed via path b).

(11) Both [2π + 2π] cycloreversions are observed as primary photoreactions in neutral BCO: Datta, P.; Goldfarb, T. D.; Boiken, R. S. *J. Am. Chem. Soc.* **1969**, *91*, 5429 and references cited therein.

(12) We thank Prof. T. Shida (Kyoto University) for pointing out this additional possibility to us and giving us a small sample of DHB for GC analyses.

(13) Upon prolonged irradiation at 405 nm $OT^{\bullet+}$ begins to appear at the expense of $COT^{\bullet+}$.

(14) If 10^{-2} M COT solutions are ionized in the same fashion, the intensity of the 505-nm band is roughly five times higher.[8a] By assuming similar ionization efficiencies for the two valence isomers we arrive at an estimate of 20% for the contribution of channel (a) to the overall photodecomposition of $BCO^{\bullet+}$.

(15) Perkin-Elmer Sigma 3B GC; 10 m × 0.5 mm ID fused silica capillary column coated with 5 μm bondend methyl phenyl (5%) silicon (16500 theoretical plates). Injection temperature 60 °C; oven temperature 4 min at 40 °C, with 30 °C/min to 90 °C, 10 min at 90 °C; detecor (FID) at 120 °C. Under these conditions, ethylene and benzene are well separated from the solvent and the C_8H_{10} isomers (BCO, COT, OT, and DHB) can be clearly distinguished. All presently relevant products were identified by separate and combined injection of spectrally well characterized authentic materials.

(16) Unfortunately, benzene exists already as a small impurity in the Freon mixture (see bottom GC trace). Nevertheless, the increase in this peak upon γ-irradiation and especially upon subsequent photolysis is evident.

(17) DHB has a ≈45 s smaller retention time than BCO under the present GC conditions[15] as indicated by the arrow in the top GC trace of Figure 2. Note that path d cannot be ruled out on spectral grounds alone since ionized DHB also shows a broad band with λ_{max} = 680 nm (T. Bally and K. Roth, unpublished results) as expected in view of λ_{max} = 635 nm in related norbornadiene(·+).[18] Upon 620-nm irradiation this band *increased* in intensity while at the same time benzene and ethylene began to appear in the thawed samples. Thus, both the [4.2.0] and the [2.2.2] isomeric cations appear to undergo photoinduced cycloreversions.

(18) Haselbach, E.; Bally, T.; Lanyiova, Z.; Baertschi, P. *Helv. Chim. Acta* **1979**, *62*, 583. In $DHB^{\bullet+}$ the first excited state is expected to lie slightly lower in energy due to the increased separation of the double bonds (I_2–I_1 is 0.28 eV less in DHB than in norbornadiene).

(19) This experiment was carried out in an argon matrix in order to be able to follow the decay of BCO in the infrared. After 4 h of photolysis at 260 nm all bands of BCO had disappeared and were replaced by those of benzene, ethylene, and OT.[11]

(20) Up to ≈3 × 10^{-2} M the intensity of the 680-nm band varies linearly with the benzene concentration. Above 3 × 10^{-2} M, the CR absorption of $(BZ)_2^{\bullet+}$ begins to grow at the expense of the 680-nm band (see spectrum in Figure 3b). The ethylene concentration was not varied because it could not be determined with sufficient precision and reliability to draw meaningful conclusions.

(21) Note that the appearance of the 680-nm band in ionized benzene + ethylene solutions might also imply (partial) formation of $DHB^{\bullet+}$.[12,17] While we cannot rigorously rule out this possibility we note that the photochemical behavior of the species formed in the benzene + ethylene experiments differs significantly from that obtained from ionized DHB in that no increase in the 680-nm band intensity is observed upon 640-nm irradiation. Further investigations aimed at clarifying the above question are in progress.

(22) Note that ΔH_D for $(BZ)_2^{\bullet+}$ and $(ET)_2^{\bullet+}$ are very similar,[23] which may be taken as an indication that ΔH_{res} and hence the related E_{CR} do also not change very much for the two complexes. On the other hand, a referee pointed out that $0.5E_{CR}$ of either $(BZ)_2^{\bullet+}$ or $(ET)_2^{\bullet+}$ must be regarded as an upper limit for the interaction energy in $(BZ{\cdot}ET)^{\bullet+}$ since ΔH_{res} decreases with increasing ionization potential difference.

(23) $\Delta H_D((BZ)_2^{\bullet+})$ = 15.3 ± 0.9 kcal/mol (Grover, J. R.; Walters, E. A.; Hui, E. T. *J. Phys. Chem.* **1987**, *91*, 3233); $\Delta H_D((ET)_2^{\bullet+})$ = 15.8 ± 1 kcal/mol (Ono, Y; Linn, S. H.; Tzeng, W. B.; Ng, C. Y. *J. Chem. Phys.* **1984**, *80*, 1482).