Electron Delocalization in Helical Quinone Anion Radicals

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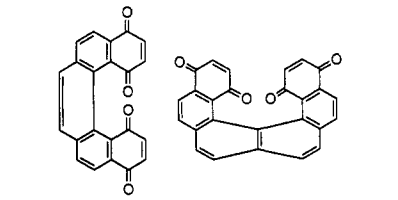
Molecules with connected functional groups that differ only in their states of oxidation, so-called mixed-valence compounds, often exhibit unusual properties.[1] This communication reports the first such molecules that are helical. The properties of the anion radicals of bisquinones **1**–**4**, which include electronic transitions at particularly long wavelengths (greater than 2 μ), indicate that electrons are delocalized throughout. In linear analogues they are localized.[2] The reason may be that the proximity of the helical array's extremities allows electrons to move easily between the ends and therefore cyclically through the array.



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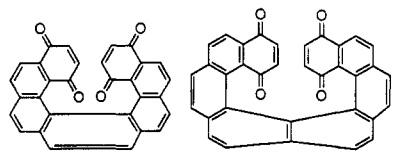
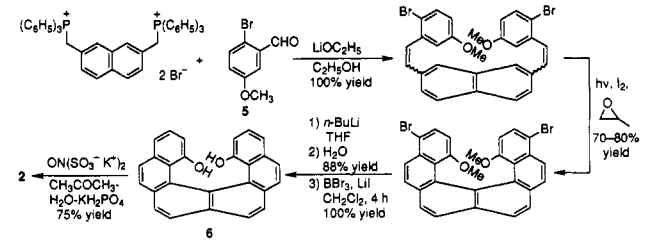


3 4

Quinone **1** was prepared by combining *p*-divinylbenzene with *p*-benzoquinone,[3] while **2** was obtained[4,5] by oxidizing **6** (Scheme I) with Fremy's salt $[ON(SO_3^-K^+)_2]$.[6] Quinones **3**[4,5] and **4**[4,5] were, like **2**, prepared by oxidizing phenols,[7] analogues of **6** that also derive from the key intermediate **5**. For **3** an alternative and preferable synthesis is outlined in Scheme II.[9]

Three points are noteworthy: (1) stoichiometric amounts of iodine and propylene oxide are essential for the photocyclizations to succeed,[10] (2) the tetraol reduction-product of **2** does not give **2** on oxidation,[11] and (3) the strategy used to synthesize **4** has not previously been used to synthesize an [8]helicene.[12]

Scheme I



Scheme II

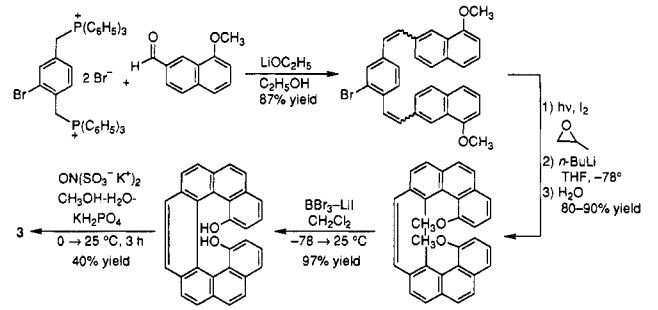


Table I. Reduction Potentials of **1**–**4** and Electronic Absorption Maxima of $\mathbf{1}^{\bullet-}$–$\mathbf{4}^{\bullet-}$[a]

anion	$-E^\circ_1$ (V)	$-E^\circ_2$ (V)	ΔE^b (mV)	λ_{max} (nm) (log ϵ)
$\mathbf{1}^{\bullet-}$	0.44	0.91	470	1400 (3.32), 590 (3.40), 420 (3.64)
$\mathbf{2}^{\bullet-}$	0.56	0.94	380	1825 (2.70), 680 (3.48), 340 (3.92)
$\mathbf{3}^{\bullet-}$	0.56	0.87	310	2200 (3.32), 580 (3.34)
$\mathbf{4}^{\bullet-}$	0.61	0.88	270	2200 (3.32), 800 (3.26), 530 (3.48)

[a] In DMF, 0.1 M Bu_4NBF_4. E° is the average of the anodic and cathodic peak potentials vs SCE. [b] $E^\circ_1 - E^\circ_2$.

When electrolyzed, each quinone is reduced in steps at the potentials recorded in Table I. Cyclic voltammetry (using solutions in DMF containing 0.1 M $Bu_4N^+BF_4^-$, a glassy carbon working-electrode, and an SCE reference) measured these potentials and showed the reductions to be reversible.[13] The anion radicals formed by passing 0.8 Faradays per mol at constant voltage through these solutions (under nitrogen, in a two-compartment cell with a carbon cathode) exhibit well-resolved ESR spectra. For $\mathbf{1}^{\bullet-}$, four of the five pairs of hyperfine splittings were resolved (a_H = 2.0, 0.73, 0.55, and 0.16 G), and the spectrum did not change as the temperature varied from 220 to 360 K. The pairing implies that the odd electron delocalizes between the two parts of the molecule in less than a nanosecond.

The electronic absorptions exhibited by solutions of the anion radicals, also recorded in Table I, each include a prominent peak in the near-IR or, in the case of $\mathbf{3}^{\bullet-}$ and $\mathbf{4}^{\bullet-}$, in the infrared, at 2.2 μ.[14] Experiments with $\mathbf{1}^{\bullet-}$ showed that the position of the near-IR absorption maximum does not change appreciably when the solvent is changed, implying that the charge is distributed symmetrically between the molecule's halves.[2d,16] (The peak is

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(1) (a) Robin, M. B.; Day, P. *Adv. Inorg. Chem. Radiochem.* **1967**, *10*, 247. (b) Allen, G. C.; Hush, N. S. *Prog. Inorg. Chem.* **1967**, *8*, 357. (c) Hush, N. S. *Prog. Inorg. Chem.* **1967**, *8*, 391. (d) Creutz, C. *Prog. Inorg. Chem.* **1983**, *30*, 1.

(2) (a) Rak, S. F.; Jozefiak, T. H.; Miller, L. L. *J. Org. Chem.* **1990**, *55*, 4794. (b) Almlöf, J. E.; Feyereisen, M. W.; Jozefiak, T. H.; Miller, L. L. *J. Am. Chem. Soc.* **1990**, *112*, 1206. (c) Jozefiak, T. H.; Almlöf, J. E.; Feyereisen, M. W.; Miller, L. L. *J. Am. Chem. Soc.* **1989**, *111*, 4105. (d) Jozefiak, T. H.; Miller, L. L. *J. Am. Chem. Soc.* **1987**, *109*, 6560.

(3) Liu, L.; Katz, T. J. *Tetrahedron Lett.* **1990**, 3983.

(4) Red solid, mp > 280 °C.

(5) The ^1H NMR, ^{13}C NMR, and HRMS accord with the structure assigned.

(6) (a) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229. (b) Buddenberg, O. In *Methoden der organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1981; Vol. IV/1a.

(7) Oxygen plus cobalt(tetraphenylporphyrin) and pyridine in benzene was used for the oxidation that gives **4**.[8]

(8) Frostin-Rio, M.; Pujol, D.; Bied-Charreton, C.; Perrée-Fauvet, M.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1971.

(9) Analogies: (a) Sudhakar, A.; Katz, T. J.; Yang, B. *J. Am. Chem. Soc.* **1986**, *108*, 2790. (b) Sudhakar, A.; Katz, T. J. *Tetrahedron Lett.* **1986**, *27*, 2231.

(10) Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769.

(11) It gives a structure that is the formal pinacol reduction-product of **2**, presumably because the valences at the para carbons can couple when the phenolic groups oxidized are on the outside.

(12) Laarhoven, W. H.; Prinsen, W. J. C. *Top. Curr. Chem.* **1984**, *125*, 63.

(13) The anodic and cathodic peaks exhibited currents that were equal and potentials that differed by 60 mV and did not vary with scan rate (20–1000 mV s^{-1}).

(14) This is a longer wavelength than for any linear analogue.[2] It is comparable to absorptions characteristic of charge-transfer complexes that are good conductors.[15]

(15) Torrance, J. B.; Mayerle, J. J.; Lee, V. Y.; Bechgaard, K. *J. Am. Chem. Soc.* **1979**, *101*, 4747.

(16) (a) Powers, M. J.; Meyer, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 4393. (b) Tom, G. M.; Creutz, C.; Taube, H. *J. Am. Chem. Soc.* **1974**, *96*, 7827.

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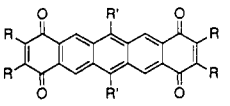
at 1.40 μ in DMF, 1.35 μ in CH_2Cl_2, and 1.42 μ in methyltetrahydrofuran.)

The contrasts between linear and helical bisquinones are striking. Unlike $\mathbf{1}^{\bullet-}$, $\mathbf{7a}^{\bullet-}$ and $\mathbf{7b}^{\bullet-}$ exhibit no well-defined absorption in the near-IR.[2c] For **7a** the difference between the first and second reduction potentials (120 mV) is one-quarter that of **1**.[2c] For $\mathbf{7b}^{\bullet-}$ the ESR spectrum changes with temperature, demonstrating that an electron localized on one quinone hops to the other with rate constant $k = 6 \times 10^8\ s^{-1}$ at room temperature.[17] That the anion radicals of all the helical quinones, not just that of **1**, have delocalized structures (unlike the linear analogues, for which this is true for only the two lowest members[2c,d]) is suggested by ΔE in Table I decreasing monotonically but still being appreciable when the quinones are separated by six rings.[2b-d] We speculate that the differences between the helical and linear anions may originate in the ends of the helices interacting. Perhaps this constitutes a new form of cyclic delocalization.[18]



7a, R = R′ = H
7b, R = CH_3; R′ = n-C_6H_{13}

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Supplementary Material Available: The sources of materials used in the syntheses (1 page). Ordering information is given on any current masthead page.

(17) Unpublished results of Stanton Rak, University of Minnesota. This derivative was used because it is more soluble than **7a**.

(18) Initial semiempirical and ab initio calculations support this hypothesis. Unpublished results of C. A. Liberko and private communication from J. Almlöf.

Synthesis and DNA Cross-Linking by a Rigid CPI Dimer

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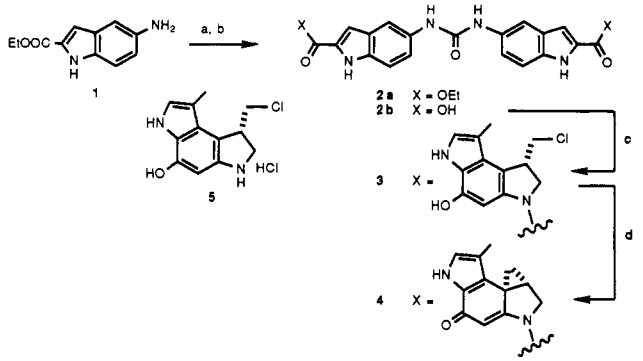
Recently, the preparation of dimeric molecules containing two of the DNA-alkylating cyclopropa[*c*]pyrrolo[3,2-*e*]indol-4-(5*H*)-one (CPI) subunits of CC-1065 was reported by these laboratories.[1] In those CPI dimers the two alkylating subunits were linked by variable-length flexible methylene chains. We anticipated that incorporation of a more rigid linker into the CPI dimers would yield molecules with a fixed, measurable recognition-site size. We report herein the synthesis of compound **3** and the corresponding spirocyclopropyl, CPI analogue, **4**.[2] We also report our preliminary biochemical efforts which (1) document the formation of interstrand cross-links by compound **3** under mild conditions and (2) begin to characterize the alkylation-site requirements for cross-linking by this compound. These compounds represent the first molecules reported as interstrand cross-linking agents with an alkylation-site size as long as six base pairs and, therefore, may serve as useful molecules on which to build our understanding of DNA as a receptor for dimeric molecules.

Scheme I[a]



[a] (a) ClCOCl, $(i\text{-Pr})_2$NEt, DMAP, THF, −98 → 0 °C, 16 h; (b) NaOH, H_2O, H_2O, pyr, 25 °C for 96 h, then 55 °C for 7 h; (c) EDC, DMA, **5** (2 equiv), 25 °C, 2 h; (d) Et_3N–H_2O–CH_3CN, 1:1:2, 40 min.

Compounds **3** and **4** both contain a bis(indolecarboxylic acid) linker, **2b**, and were prepared as shown in Scheme I.[3] Briefly, amine **1**[4] was converted to its symmetrical urea **2a** by treatment with phosgene at low temperature. The resultant diester **2a** was hydrolyzed to the diacid **2b** with aqueous sodium hydroxide in pyridine at 25 °C. Bis(chloromethyl)diphenol **3** was prepared from **2b** and cyclized to bis(cyclopropapyrroloindole) **4** by previously described methodology.[1,5]

Compound **3**, presumably serving as a ring-opened prodrug of **4**, readily alkylates DNA and possesses cytotoxic properties similar to those of the spirocyclopropyl compound **4**.[6] The method of induced circular dichroism[8-10] reveals strong DNA association for both **3** and **4** consistent with their binding and bonding within the minor groove of DNA.[11] In addition, a dose-dependent formation of interstrand cross-links in ΦX174 restriction fragments treated with compound **3** is revealed by the appearance of reduced-mobility bands during denaturing alkaline agarose gel electrophoresis (supplementary material).[1] These results mimic our earlier observations, that interstrand cross-linking can be correlated with high cytotoxic potency for CPI dimers.[1] In contrast to the flexible CPI dimers, compound **3** exhibits curative in vivo antitumor efficacy in some systems.[12]

Considerable effort has been expended to understand the details of the interaction between monomeric CPI compounds and DNA in an attempt to gain insights into their interesting biological properties.[8,10,13,14] Molecular modeling studies with compound

(1) Mitchell, M. A.; Johnson, P. D.; Williams, M. G.; Aristoff, P. A. *J. Am. Chem. Soc.* **1989**, *111*, 6428-6429.

(2) Compound **3**, NSC 615291, also referred to as U-77779, is currently under development in collaboration with the National Cancer Institute.

(3) Analytical data for compounds **2a**,**b**, **3**, and **4** are consistent with the structures shown. See supplementary material.

(4) Warpehoski, M. A.; Bradford, V. S. *Tetrahedron Lett.* **1988**, *29*, 131-134.

(5) Kelly, R. C.; Gebhard, I.; Wicnienski, N.; Aristoff, P. A.; Johnson, P. D.; Martin, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 6837-6838.

(6) Compounds **3** and **4** each inhibit the growth of murine L1210 leukemia cells by 50% at a concentration of 1 pM in a 3-day in vitro assay.[7]

(7) For comparison, the IC_{50}'s for CC-1065 and adozelesin are 30 and 4 pM respectively.

(8) Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovren, J. P.; Prairie, M. D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590-603.

(9) Krueger, W. C.; Li, L. H.; Moscowitz, A.; Prairie, M. D.; Petzold, G.; Swenson, D. H. *Biopolymers* **1985**, *24*, 1549-1572.

(10) (a) Li, L. H.; Swenson, D. H.; Schpok, S.; Kuentzel, S. L.; Dayton, B. D.; Krueger, W. C. *Cancer Res.* **1982**, *42*, 999-1004. (b) Bhuyan, B. K.; Newell, K. A.; Crampton, S. L.; Von Hoff, D. D. *Cancer Res.* **1982**, *42*, 3532-3537. (c) Li, L. H.; Wallace, T. L.; DeKoning, T. F.; Warpehoski, M. A.; Kelly, R. C.; Prairie, M. D.; Krueger, W. C. *Invest. New Drugs* **1987**, *5*, 329-337.

(11) Unpublished results.

(12) For example, the most effective flexible dimers (spirocyclopropyl or chlorophenol form) increased the life span of mice bearing intraperitoneal L1210 leukemia by 60-80% at optimal iv doses while a single iv injection of compound **3** at 10 μg/kg cured (30 day survivors) 50% of the mice. For comparison, adozelesin increased the life span of such mice by 94% at an optimal single iv dose of 100 μg with no cures. Results of additional antitumor testing with compound **3** will be reported separately.

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