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Abstraction of Deuterium from Dideuteroglycine by Aryl Radical: A Model for 1,4-Benzene Diradical Reactions with Proteins

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Abstract: Aryl radicals are generated by oxidation of aryl hydrazine with PbO_2 or via photolysis of aryl iodide. Abstraction of deuterium from dideuteroglycine derivatives is demonstrated as a model for the possible reaction of 1,4-aryl diradicals with amino acid residues in proteins.

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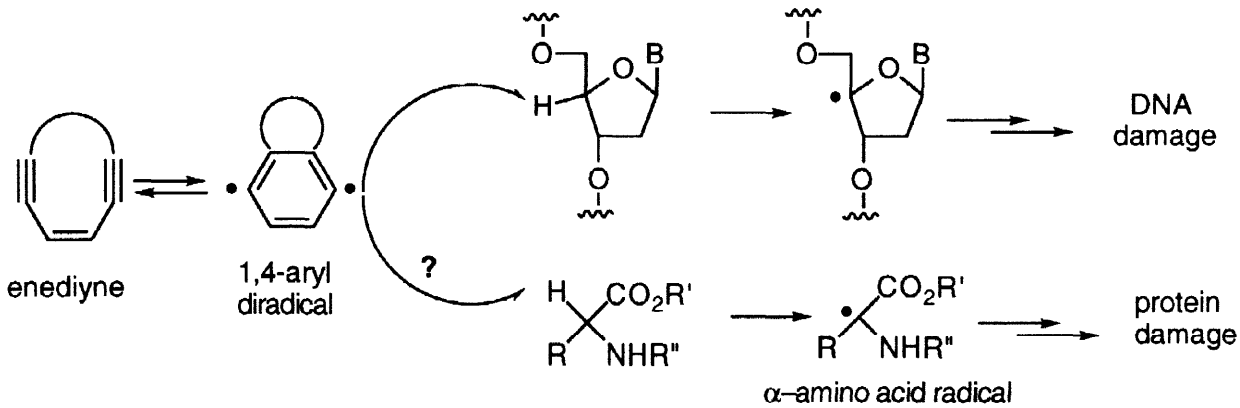
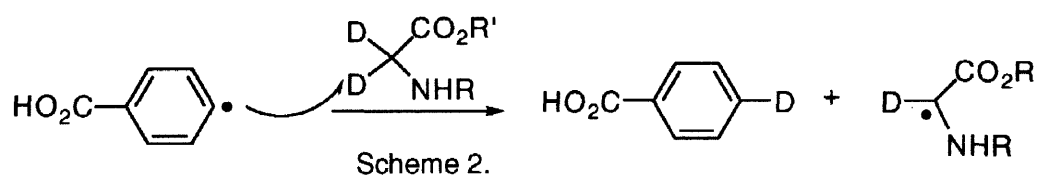
The enediyne class of antibiotics[1] are potent anti-tumor agents that generally target DNA; however, evidence exists for agglomeration of proteins[2] by the enediyne chromophores and their apoproteins. Considering the low bond dissociation energy of peptidyl α-carbon hydrogen bonds,[3,4] it seems likely that abstraction of hydrogen from this position by a 1,4-benzene diradical should be a favorable process. In order to demonstrate the feasibility of this process in a simple



Scheme 1.

model system, aryl monoradicals[5] were allowed to react with dideuteroglycine derivatives (Scheme 2). The parent 1,4-benzene diradical is slightly less reactive than phenyl radical: at room temperature the 1,4-diradical has been calculated to react 14 times more slowly than phenyl radical in abstraction of a methyl hydrogen from methanol.[6] Experimentally 9,10-dehydroanthracenyl biradical abstracts hydrogen 100-200 times slower than phenyl radical.[7] For ease of synthetic manipulation and product isolation, *p*-benzoic acid radicals were chosen for



Scheme 2.

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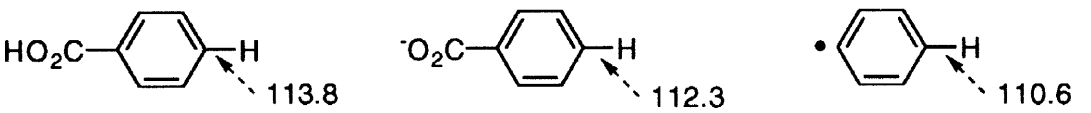
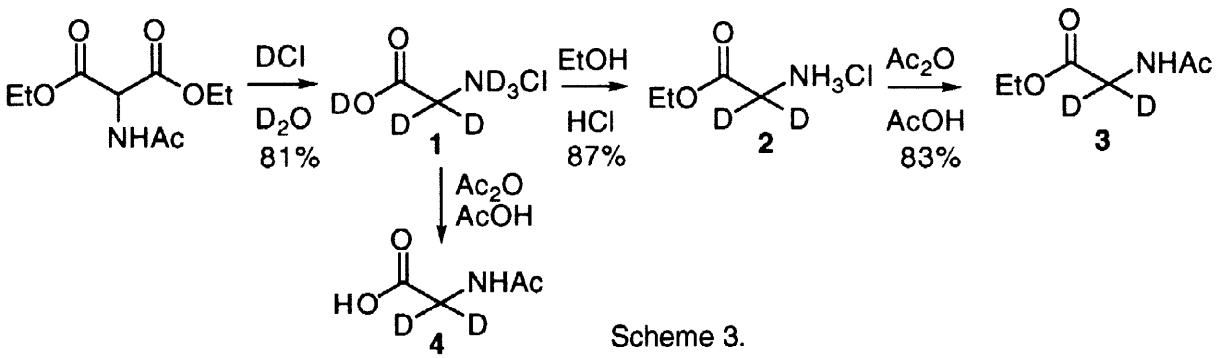
this study. Aryl substitution does affect the reactivity and rate of hydrogen abstraction by aryl radicals.[8] A carboxylic acid or carboxylate substituent is calculated to result in a bond dissociation energy of the *p*-hydrogen of 113.8 kcal/mol and 112.3 kcal/mol respectively,[9] compared to the experimental bond dissociation energy value of 110.6 ± 3.4 for the *p*-hydrogen of phenyl radical[10] in the gas phase.



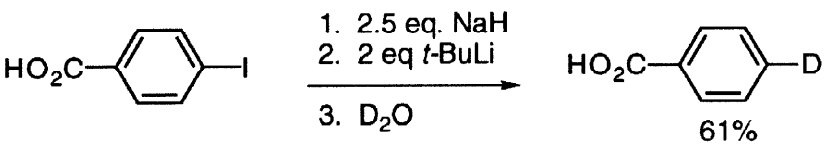
Gas Phase Bond Dissociation Energies[9,10] (kcal/mole)

The dideuteroglycine derivatives were prepared with excellent levels of deuterium incorporation starting with diethyl acetamidomalonate.[11] Decarboxylation in acidic deuterium oxide gave α-D_2 glycine **1**. Esterification provided **2** which showed 97% deuterium incorporation from the preceding step by ^{1}H-NMR integration. Acetylation provided the organic soluble *N*-acetyl



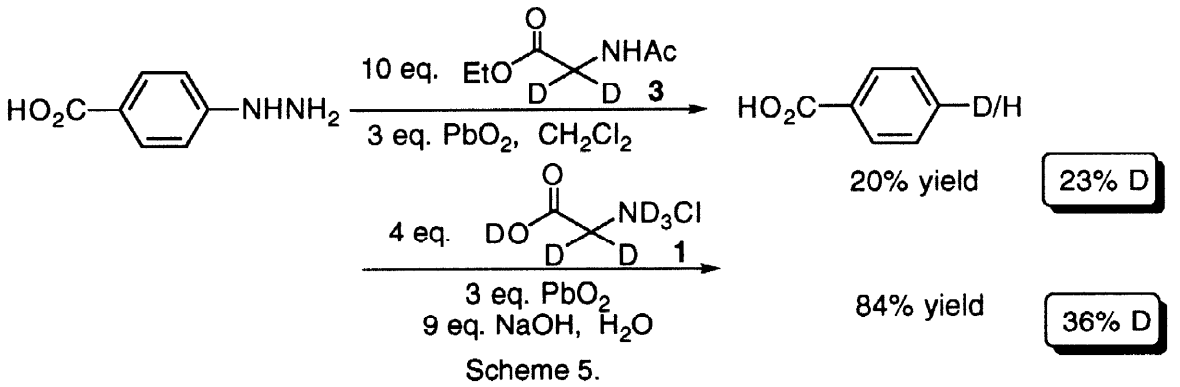
Scheme 3.

α-D_2 glycine ethyl ester **3** or free acid **4**. For spectroscopic comparison, a sample of authentic 4-*D*-benzoic acid was prepared from 4-iodobenzoic acid by initial deprotonation of the carboxylic acid with sodium hydride, followed by metal-halogen exchange of the aryl iodide with *t*-BuLi and subsequent quenching with D_2O (Scheme 4).



Scheme 4.

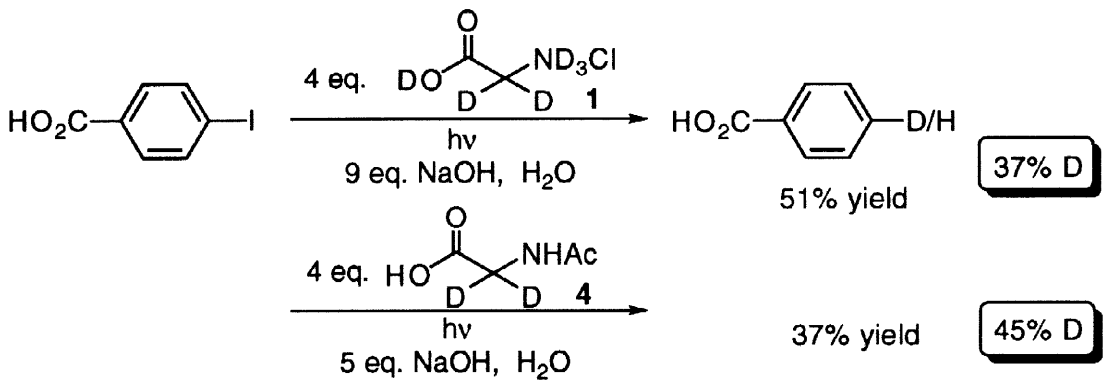
Aryl radicals were generated by two different methods: the commercially available 4-hydrazinobenzoic acid was oxidized with lead dioxide[12] at RT or 4-iodobenzoic acid was subjected to photolysis, under either organic or deoxygenated aqueous conditions. The benzoic acid product was isolated by acidification followed by extraction with diethyl ether,[13] and the amount of deuterium incorporation was determined by ^{1}H-NMR integration.[14] Deuterium incorporation was confirmed by ^{2}H-NMR. The initial hydrogen abstraction experiments using the lead dioxide, hydrazine methodology gave 23% deuterium incorporation in the benzoic acid



Scheme 5.

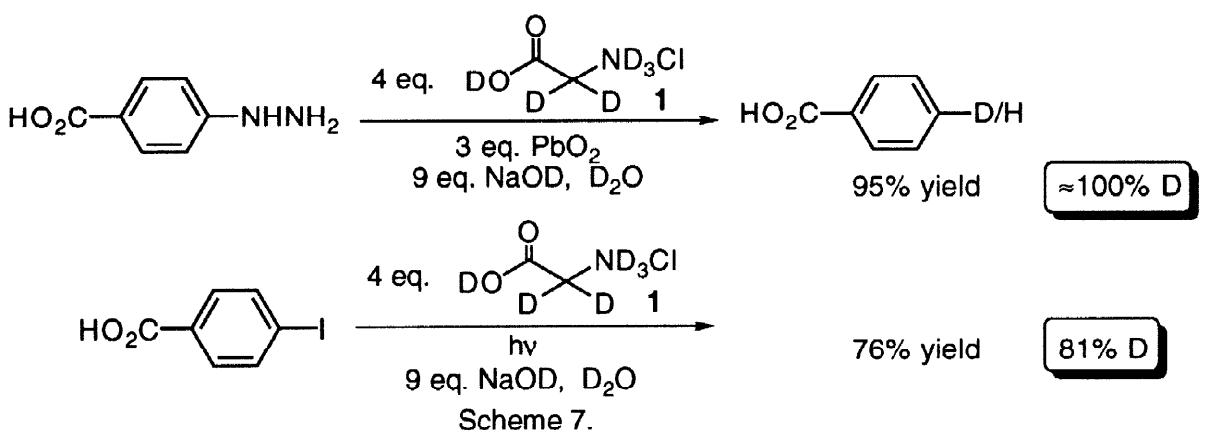
product in organic solvent, and 36% deuteration under basic aqueous conditions (Scheme 5).

Photolysis with a low pressure Hg arc lamp at 254 nm generated aryl radicals in basic aqueous solution (Scheme 6). Next, acetylated dideuteroglycine **4** was utilized to discourage a possible SET mechanism between the electron poor aryl iodide and the amine group of the amino acid. Deuterium incorporation was somewhat improved with the acetylated substrate.



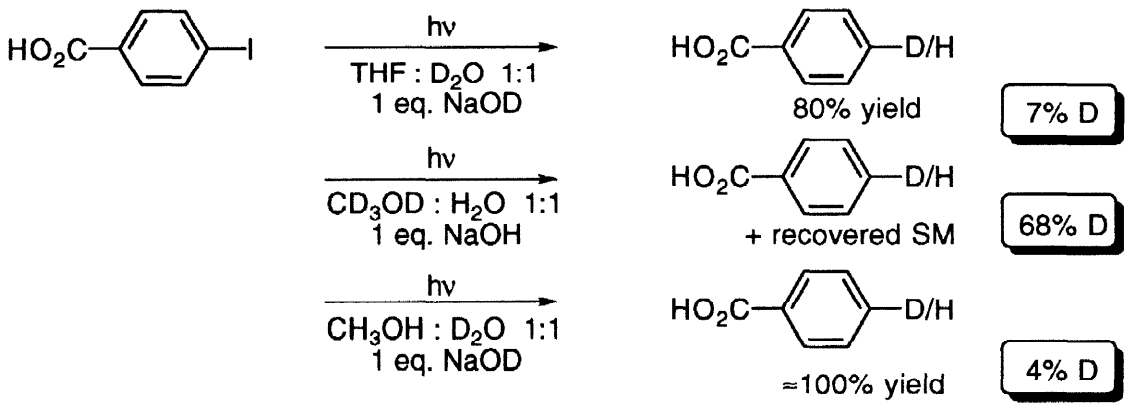
Scheme 6.

The kinetic isotope effect is expected to somewhat impede the incorporation of the deuterium label into the benzoic acid product, however the source of the large amount of *p*-hydrogen that is incorporated is puzzling. Several control reactions were carried out. In order to check the integrity of the deuterated reagents, two reactions were run using all deuterated reagents (Scheme 7).



Scheme 7.

Deuterium incorporation in these experiments was high. The role of the solvent as either a hydrogen atom or proton donor was next examined by running control reactions in the absence of a deuteroglycine derivative (Scheme 8). In each case, a relatively good hydrogen atom donor (THF or MeOH) or deuterium atom donor (CD_3OD) was responsible for the majority of the hydrogen or deuterium incorporation[15] at the *p*-position of benzoic acid, however there is some "leakage," implying a background *ionic* route for deuterium or hydrogen incorporation.



Scheme 8.

In summary, aryl radicals have been demonstrated to abstract deuterium from the α-position of dideuteroglycine derivatives. These abstractions have biological implications as a model for the reactions of 1,4-benzene diradicals derived from enediyne antitumor antibiotics with proteins.

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14. Error in the ^{1}H-NMR integration at 500 MHz is estimated at ±5%. Deuteration in the benzoic acid products was confirmed by ^{2}H-NMR: (in $CHCl_3$; δ = 7.65 ppm).
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