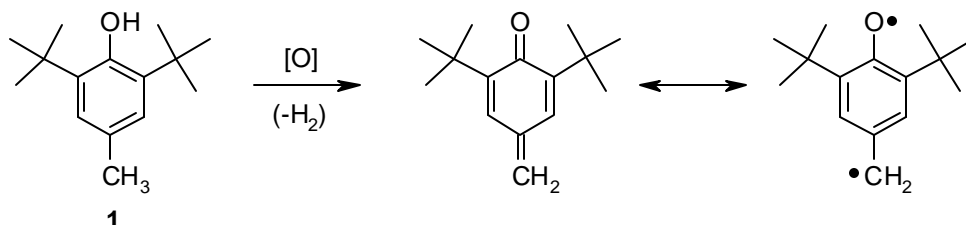


Kinetic Studies of Quinone Methides and Amines

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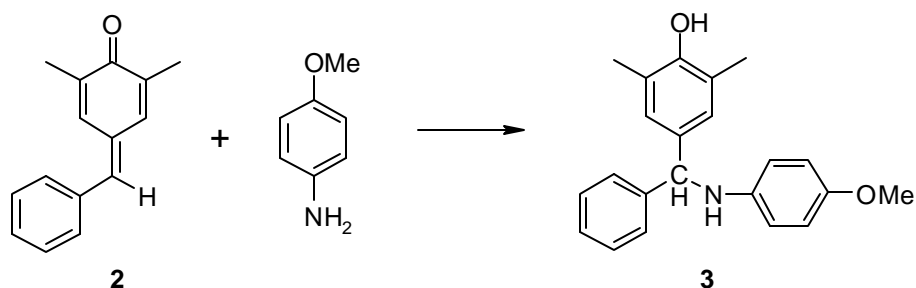
Quinone methides (QMs) are a class of reactive intermediates that are of interest as toxins found or metabolically formed from spices, food additives and drugs. They have been shown to react with biological nucleophiles such as DNA and proteins. The widely-used food additive butylated hydroxytoluene (BHT) (**1**), is thought to metabolize to a quinone methide and is a possible carcinogen.



The QM shown below (**2**) was synthesized in the lab and its reactivity is being studied. This particular QM was chosen as it can be isolated as a stable yellow solid. Kinetic studies were done to examine the quenching effects of various amine nucleophiles on the QM. QM was injected into buffered aqueous solutions and its decay rate was determined using UV spectroscopy. A Brønsted-like plot was constructed in order to establish the correlation between reactivity and basicity of the nucleophile. It was found that although closely related compounds showed some linear dependency on pK_a's, the plot was a scatter plot. Overall, however, amines were shown to be highly reactive towards the QM even in low concentrations, and were able to compete effectively with hydrolysis.

Phenol was also studied as a nucleophile. Although an adduct was formed quickly with the QM, this reaction was reversible and the water reaction could also be observed using longer time scales, with the QM alcohol being the final product.

Several stable QM-amine adducts were isolated and characterized by ¹H and ¹³C NMR, and mass spectroscopy. Compound **3** is the *para*-anisidine quinone methide adduct which was isolated:



The data for the reactivity of the various amines studied supports the hypothesis that QM adds preferentially to exocyclic NH₂ groups of the DNA heterocycles. It also suggests that basicity is not the predominant factor dictating the reactivity of amines with QM's.