CHM 202 – Problem of the week

Rofecoxib (Vioxx®) is a cyclooxygenase-2 inhibitor (COX-2 is the enzyme which mediates the body's response to arthritis and other inflammatory conditions). Unfortunately, recent studies have indicated that Vioxx® can cause dramatic increases in blood pressure and is linked to a variety of heart malfunctions. *The molecule is also unusually acidic.* Loss of a proton, as shown below, affords a conjugate base (**A**) that immediately and irreversibly reacts with a number of biological methylating agents (CH_3-X, see reaction scheme below).

a) Explain why Rofecoxib is so much more acidic than typical hydrocarbons. Upon deprotonation, the conjugate base is resonance stabilized and aromatic (as shown in **B**).
b) Draw arrows to show the flow of electrons in the reaction of **A** to **B**. See below.
c) Why do you think the alkylation (think of an S_N2 reaction) occurs only on the oxygen and not at the site of proton removal (on the carbon)? With O-alkylation, a methoxyfuran can form which again is aromatic. Methylating at carbon will give the unsaturated lactone which is non-aromatic
d) Draw the *exo* adduct that occurs when furan **B** reacts with propenal (you may replace the phenyl rings with "Ar"). Diels-Alder adduct will have the OCH_3 and CHO groups on adjacent carbons.