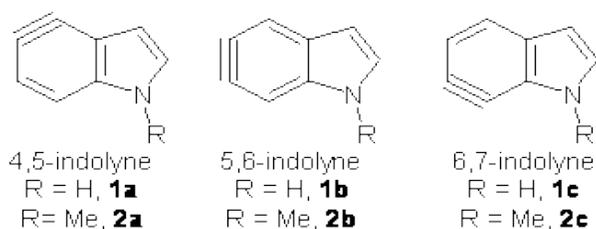


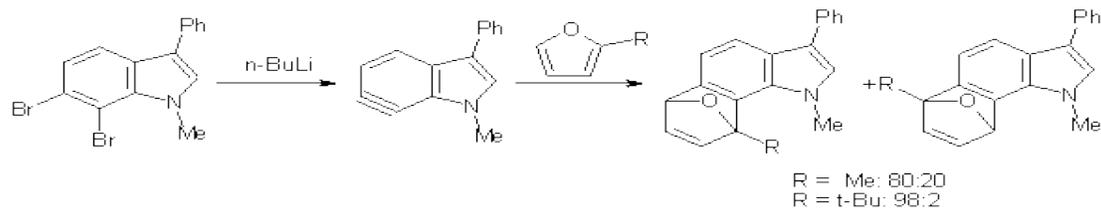
INDOLYNE REGIOSELECTIVITY EXPLAINED

The nature of reactions of indolynes is the subject of two recent computational/experimental studies. There are three isomeric indolynes **1a-c** which are analogues of the more famous benzyne (which I discuss in significant detail in Chapter 4.4 of my book).



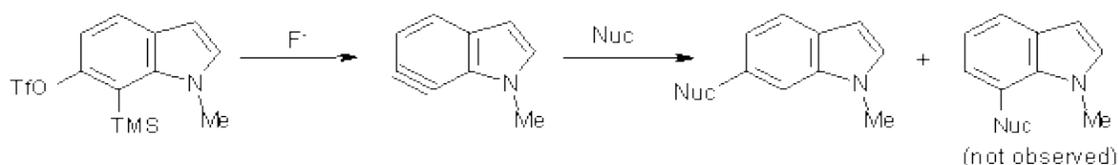
One might anticipate that the indolynes undergo comparable reactions as benzyne, like Diels-Alder reactions and nucleophilic attack. In fact the indolynes do undergo these reactions, with unusual regioselectivity. For example, the reaction of the substituted 6,7-indolyne undergoes regioselective Diels-Alder cycloaddition with substituted furans (Scheme 1), but the reaction with the other indolynes gives no regioselection.¹ Note that the preferred product is the more sterically congested adduct.

Scheme 1



In the case of nucleophilic addition, the nucleophiles add specifically to C₆ with substituted 6,7-indolynes (Scheme 2), while addition to 4,5-indolynes preferentially gives the C₅-adduct (greater than 3:1) while addition to the 5,6-indolynes preferentially gives the C₅-adduct, but with small selectivity (less than 3:1).²

Scheme 2



The authors of both papers – Chris Cramer studied the Diels-Alder chemistry and Ken Houk studied the nucleophilic reactions – employed DFT computations to examine the activation barriers leading to the two regioisomeric products. So for example, Figure 1 shows the two transition states for the reaction of **2c** with 2-*iso*-propyl furan computed at MO6-2X/6-311+G(2df,p).

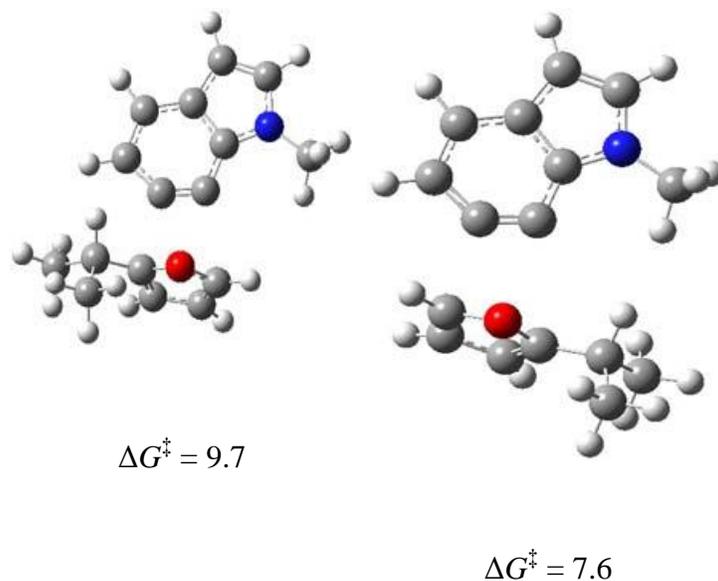


Figure 1. MO6-21/6-311+G(2df,p) optimized TSs for the reaction of 2-*iso*-propylfuran with **2c**. Activation energy (kcal mol⁻¹) listed below each structure.¹

The computational results are completely consistent with the experiments. For the Diels-Alder reaction of 2-*t*-butylfuran with the three indolynes **2a-c**, the lower computed TS always corresponds with the experimentally observed major product. The difference in the energy of the TSs leading to the two regioisomers for reaction with **2a** and **2b** is small (less than 1 kcal mol⁻¹), consistent with the small selectivity. On the other hand, no barrier could be found for the reaction of 2-*t*-butylfuran with **2c** that leads to the major product. Similar results are also obtained for the nucleophilic addition – in all cases, the experimentally observed major product corresponds with the lower computed activation barrier.

So what accounts for the regioselectivity? Both papers make the same argument, though couched in slightly different terms. Houk argues in terms of distortion energy – the energy needed to distort reactants to their geometries in the TS. As seen in Figure 2, the benzyne fragment of **2a** is distorted, with the C-C-C angle at C₄ of 125° and at C₅ of 129°. In the transition states, the angle at the point of nucleophilic attack widens. Since the angle starts out wider at C₅, attack there is preferred, since less distortion is needed to achieve the geometry of the TS.

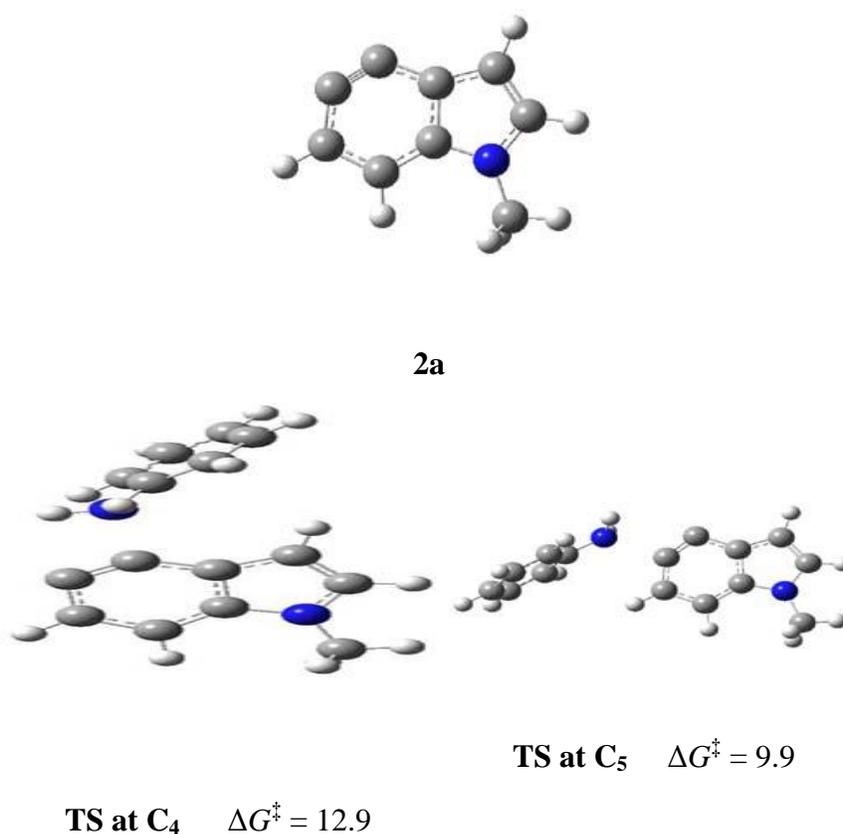


Figure 2. B3LYP/6-31G(d) optimized structures of **2a** and the TSs for the reaction of aniline with **2a**. Activation energy in kcal mol⁻¹.²

Cramer argues in terms of the indolyne acting as an electrophile. Increasing substitution at the furan 2-position makes it better at stabilizing incipient positive charge that will build up there during a (very) asymmetric Diels-Alder transition state. This explains the increasing selectivity of the furan with increasing substitution. The indolyne acting as an electrophile means that the attack will lead from the center with lesser charge. In **2c**, the C-C-C angle at C₆ is 135.3°, while that at C₇ is 117.2°. This makes C₇ more carbanionic and C₆ more carbocationic; therefore, the first bond made is to C₆, leading to the more sterically congested product. Note that Houk's argument applies equally well, as C₆ is pre-distorted to the TS geometry.

Source: <http://comporgchem.com/blog/?p=759>