

[P19] The Donor-Acceptor Dichotomy of Isocyanides as Stereoelectronic Chameleons in Radical Additions

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One of the reasons why isocyanides are often the reagents of choice for initiation of radical cascades is their high chemoselectivity of intermolecular radical reactions of this group with a variety of radical sources in the presence of multiple reactive functionalities. [1] Our goal was to explain such reactivity. The high exothermicity of this process contributes to the earliness of this TS and the low activation energy. Indeed, NBO analysis identifies selective TS-stabilizing 2c,3e-interactions that account for the low activation barriers. Figure 1 shows the TS-geometry for addition of Me-radical to the C-end of the isocyanide, with CCN angle ($\sim 113.7^\circ$) for this attack slightly deviating from the Burgi-Dunitz trajectory. This correlates with the attempt to maximize overlap between isocyanide's lone pair and Me-radical orbital. The magnitude of this interaction (~ 34 kcal/mol, as evaluated by NBO analysis) suggests that it is a major electronic effect in the stabilization of this TS. The magnitude of this interaction is only slightly smaller than the combined energy of the bond-forming $p_C \rightarrow \pi_{CN}^*$ and $\pi_{CN} \rightarrow p_C$ interactions ($\sim 30+6=36$ kcal/mol). The efficiency of these intermolecular stabilizing interactions is illustrated by the negative value for activation enthalpy for this addition. The changing balance between two effects illustrates that radicals (*i.e.*, half-full/half-empty orbital systems that are, by their nature, chameleonic) can take advantage of the chameleonic properties [2] of isocyanides by amplifying either the donation to the isocyanide π_{CN}^* or accepting electron density from the isocyanide lone pair. Given the dichotomy of isocyanides as both donor and acceptor, we investigated several candidates for radical additions with an array of electronic properties.

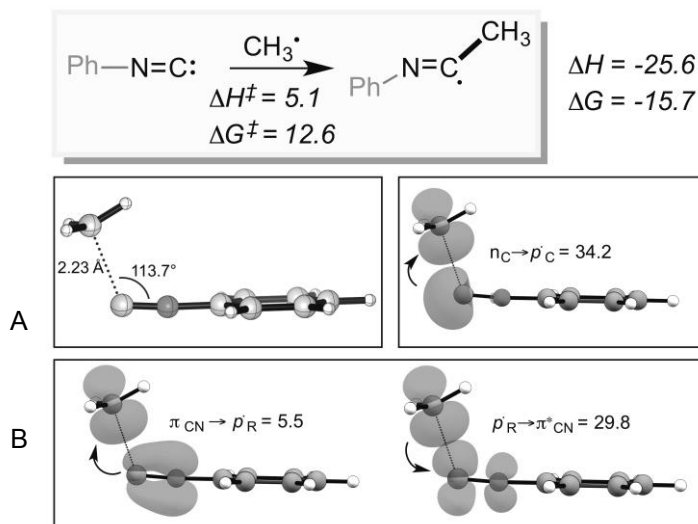


Figure 1. A. left: Transition State geometry for the methyl radical addition to isocyanide group. A. right: TS-stabilizing 2c,3e interaction between the radical and the lone pair of isocyanide. B. bond-forming radical/ π -system interactions. Orbital interactions are quantified with NBO analysis, in kcal/mol.

Bibliography:

- [1] C. J. Evoniuk, G. P. Gomes, M. Ly, F. D. White, I.V. Alabugin. *J. Org. Chem.* 82 (2017) 4265-4278.
 [2] Vatsadze, S. Z.; Loginova, Y. D.; Gomes, G.; Alabugin, I. V. *Chem. Eur. J.* 22 (2016) 3225-3245.