

Ab initio Study of Nucleophilic Aromatic Substitution of Polyfluorobenzene

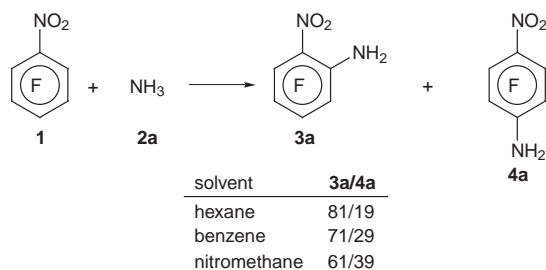
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Calculations at *ab initio* levels of theory of the nucleophilic aromatic substitution of pentafluoronitrobenzene with amines demonstrate an addition–elimination mechanism (S_NAr), with the rate-determining step at the second transition state involving C–F bond breaking, and support the *ortho*-selectivity of the reactions based on the stability of the second transition states.

Nucleophilic aromatic substitutions of polyfluoroaromatic compounds have been proposed to proceed by an addition–elimination mechanism (S_NAr) via an intermediate Meisenheimer complex (MC), where a first transition state (TS1) is assumed to, in general, determine the reaction rate, rather than a second transition state (TS2) involving a large degree of C–F bond breaking.^{1–4} Orientation in substitutions of monosubstituted pentafluorobenzenes is reported to be dependent on the substituent and theoretical interpretations are limited.^{9–12} Here, we demonstrate that *ortho*-selectivity in the nucleophilic aromatic substitutions of pentafluoronitrobenzene **1** with amines can be explained by an *ab initio* calculated reaction profile involving a two-step process with the rate-determining step at TS2.

In substitution of **1** with ammonia **2a** the preferential *ortho*-selectivity was realised in non-polar solvents and was relaxed with increasing solvent polarity¹³ (Scheme).



Scheme

Calculations at *ab initio* levels of theory, RHF/6-31G* and Becke3LYP/6-31G*, for the *ortho*-substitution show a reaction profile with formation of the second transition state **TS2-3a** being the rate-determining step (Fig. 1). The Meisenheimer complex **MC-3a** is observed to lie relatively high energy and has a shallow energy minimum. A reaction profile for the *para*-substitution, on the other hand, indicates a one step substitution path with one transition state **TS2-4a**, corresponding to the second transition state, where the Meisenheimer complex is too unstable to be optimised as a stationary state (Fig. 2). It should be noted that the initially formed π -complex (**PC-2a**) has a quite shallow minimum and is characterized by the absence of charge transfer from the ammonia nucleophile to the benzene ring. Calculations indicate that **TS2-3a** lies at a lower energy level by 6.04 kcal mol⁻¹ (RHF/6-31G*) or 7.93 kcal mol⁻¹ (Becke3LYP/6-31G*) than **TS2-4a**, which supports the *ortho*-selectivity of the reaction. The stability of **TS2-3a** is ascribed to both hydrogen bonding of the ammonia-hydrogen atom with the oxygen atom of the neighbouring nitro group and with the leaving fluorine atom. Relaxation of the *ortho*-selectivity in polar solvents is ascribed to weakened hydrogen bonding in **TS2-3a**.

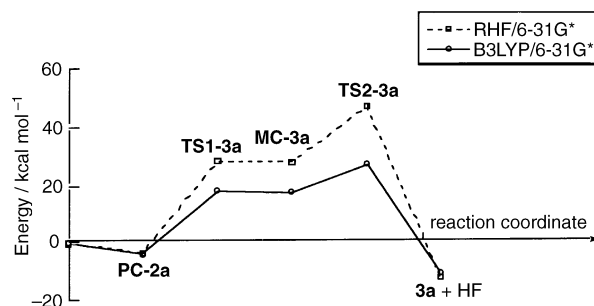


Fig. 1 *Ab initio* calculated reaction profile in *ortho*-substitution of pentafluoronitrobenzene with ammonia

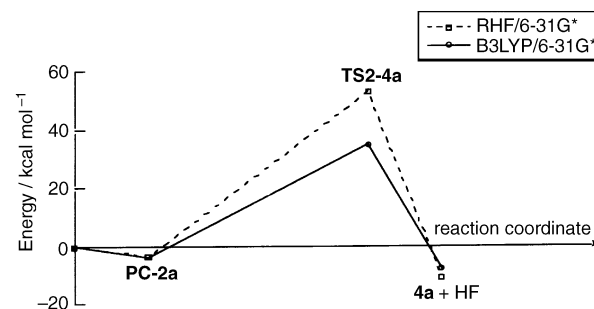


Fig. 2 *Ab initio* calculated reaction profile in *para*-substitution of pentafluoronitrobenzene with ammonia

The preferential *ortho*-selectivity in substitution with methylamine is described and is also interpreted on the basis of the *ab initio* calculations.

Techniques used: IR, ¹H and ¹⁹F NMR, *ab initio* calculations

Tables: 4 (+ 2 Supplementary Tables)

Fig. 3: Structures of π -complexes optimised at the Becke3LYP/6-31G* level

Fig. 4: PM3 optimised structures of **TS2-3a** (NH₃) and **TS2-4a** (NH₃)

Fig. 5: *Ab initio* calculated reaction profile in *ortho*-substitution of pentafluoronitrobenzene with methylamine

Fig. 6: *Ab initio* calculated reaction profile in *para*-substitution of pentafluoronitrobenzene with methylamine

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