Ab initio studies on the mechanisms of ipso-substitution observed in DA-APPI

Alexander Haack1; Clara Markert1; Tiina Kauppiälä2; Hendrik Kersten1; Thorsten Benter1

Introduction
A feasible ion/molecule reaction pathway with halobenzene dopants in diphenyl-assisted atmospheric pressure photoionization (DA-APPI) selectively adds a covalently charged phenyl-ringed to particular compound classes.1–3 Fig. 1. Systematic experimental data showed that specific criteria, such as the nucleophilicity and steric hindrance are key parameters to promote the formation of the [M+Ph]+ ion.

Computational Details
Software package: Gaussian09, Revision C.01-01 for calculations Gaussian View 4.1 for visualization
Machine: UNEX-based cluster computer, 16 core CPUS (2X8256 AMD Opteron; Advanced Micro Devices GmbH, Darmstadt, Germany) and 32x16 Gb memory
Typically 8 cores with 10 Gb memory were used for each calculation

Level of Theory:
Density Functional Theory (DFT)
B3LYP exchange correlation functional3–5
standard 6-31G(d,p) basis
Grimes’s empirical dispersion correction5–9
tight convergence criteria for geometry optimizations
ultrahigh integration grid

Calculations
Calculations (without dispersion correction): pyridine was chosen as the anucleophile (Group 1) reaction mechanism for each halobenzene (PhM, PhCl, PhBr, PhI).

Methods for Reaction Pathway:
Reactive, product and intermediate structures (SI) were guessed and optimized to a local minimum on the Potential Energy Surface (PES).S
Sims of critical coordinates were performed to initial guess of transition states (TS), which were subsequently optimized.
Frequency calculations were performed for each minimum/transition-state to confirm the desired number of negative eigenvalues.

Calculations
Search for TS and TS according to the mechanism shown above.

Results:
A weak intermediate (SI2) where the lone pair of the nitrogen is attracted to the positive charge (located mostly at C) is always observed. A transition state (TS1): follows, where pyridine breaks the system of the dopant (very low for PhI).

Thermochromy
For fluoro- and chlorobenzene a secondary intermediate (SI2) is found, where C, is in an sp hybridization (M-Dopant?).
A simultaneous cleavage of the C-X bond with formation of the C-N bond is observed for X=Br (possibly due to steric hindrance).
Subsequent cleavage of the C-X bond lacking the energy demanding for F (due to strong C-F bonding) and easy for Cl.
Overall, the reaction is thermodynamically favorable for Cl, Br, while it stops at the adduct formation for F. This is exactly what has been observed in the mass spectra.10

Question
Why is the gas-substitution observed with pyridine but not at all with pyrrole?

Calculations
Search for IS and TS according to the mechanism shown above.

Results:
TS1 is very unfavorable since two aromatic systems are destroyed simultaneously. IS2 is very similar to the TS (H and Cl are gauche according to the C-N bond).
Reaction is highly endergonic since the aromatic system of pyridine remains destroyed.
The positive charge is poorly delocalized.

Question
Which position of the oxazole attacks the halobenzene: the oxygen, the nitrogen or the carbon in between?

Calculations
Geometry optimization and thermodynamics for the three different products.

Results:
O: The two rings are orthogonal (88°). Hence there is no overlap of the n-systems in unfavorable (strongly H-bonds free reaction enthalpy, possibly poor delocalization of the positive charge in the oxazole ring).
C: The oxazole ring opens and the carbon remains in a sp configuration. Stabilization of the positive charge (mostly located at benzene position) through the oxygen in the aldheyde group and the phenyl ring.
N: Angle between rings is 44°. Hence there is an overlap between the n-systems (same in pyridine); positive charge distributed throughout the oxygen/phenyl entire ring.

Only the attack of the N-atoms leads to an energetic reaction.

Conclusion
- The calculations support the proposed mechanism of the gas-substitution. For some anilino/diphenyl combinations, an attack (M-Dopant) is formed (even the global minimum pyridine + PhI) while it is destroyed for others (pyridine + PhI).
- Depending on the position change through any type of n-system lowers the intermediate structures and products in energy and hence promotes the formation of the substitution product.
- A lone pair as nucleophile is helpful (pyridine works better than pyrrole; however, the overall reaction enthalpy also depends on factors such as the overlap of n-systems in the product (oxazole + PhI)’s work better at C than at O, depending on the nucleophile.
- Aromatic N-compounds seem to react most favorably.
- In general, the reaction is feared by increasing size of the halogen.
- Ab initio calculations supported the experimental results (each calculation shown is consistent with the experimental data). They revealed a deeper insight into the fundamental chemistry behind the observed mass spectra.

Outlook
- Intermediate structures for oxazoles will be calculated.
- Isoxazole and furan will be compared with oxazole to gain a better insight of the unfavorable oxygen attack.
- Secondary amines will be compared with tertiary amines (N/methylamide).

Literature

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