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

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Introduction

A feasible ion/molecule reaction pathway with halobenzene dopants in dopant-assisted atmospheric pressure photo ionization (DA-APPI) selectively adds a positively charged phenyl-ring to particular compound classes[1] (cf. fig. 1). Systematic experimental data revealed that specific criteria, such as the nucleophilicity and sterical hindrance are key parameters to promote the formation of the $[M+Ph]^+$ ion.

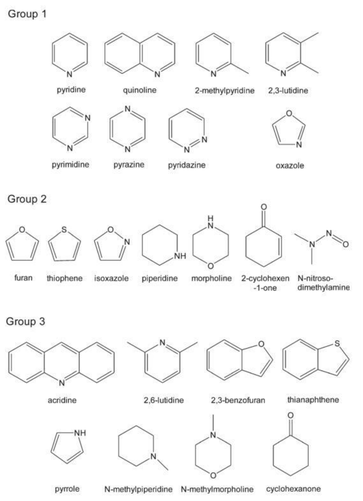


Fig. 1: Experimentally investigated compounds. Group 1: Dominating $[M+Ph]^+$ formation; Group 2: $[M+Ph]^+$ formation in less abundance; Group 3: no substitution observed.

In this contribution the experimental observations are further investigated with ab initio calculations to provide a deeper understanding of the critical chemical properties of the analyte which lead to the formation of the substitution product. The impact of the halogen-type and the single reaction steps along the proposed pathway are investigated as well.

Computational Details

Software package:

Gaussian09, Revision C.01 [2] for calculations

GaussView 4.1 [3] for visualization

Machine:

UNIX-based computer cluster, 4×16-Core CPUs (6282SE AMD Opteron; Advanced Micro Devices GmbH, Dornach, Germany) and 32×16 GB memory

Typically 8 cores with 10 GB memory were used for each calculation

Calculation Methods

Level of Theory:

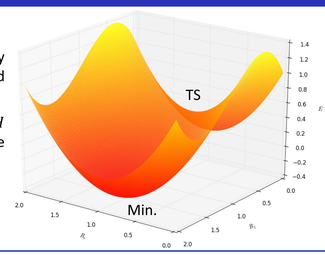
- Density Functional Theory (DFT)
- B3LYP exchange correlation functional[4,5]
- standard Pople 6-311+G(df,2p) basis[6]
- Grimme's empirical dispersion correction[7]
- tight convergence criteria for geometry optimizations
- ultrafine integration grid

Methods for Reaction Pathway:

- Reactant, product and intermediate structures (IS) were guessed and optimized to a local minimum on the Potential Energy Surface (PES).
- Scans of critical coordinates were performed to propose initial guesses of transition states (TS), which were subsequently optimized.
- Frequency calculations were performed for each minimum/first-order-saddle-point to confirm the desired number of negative eigenvalues.

Thermochemistry:

- For stable structures, the corrections to the enthalpy H_{corr} and the Gibbs free enthalpy G_{corr} were calculated from the partition functions.
- With the electronic energy ε_0 the reaction enthalpy $\Delta_R H$ and the Gibbs free reaction enthalpy $\Delta_R G$ can be calculated according to:
- $\Delta_R H = \sum_{products}(\varepsilon_0 + H_{corr}) - \sum_{reactants}(\varepsilon_0 + H_{corr})$
- $\Delta_R G = \sum_{products}(\varepsilon_0 + G_{corr}) - \sum_{reactants}(\varepsilon_0 + G_{corr})$



Min. and TS: $\frac{\partial E}{\partial R_i} = 0 \quad \forall i$

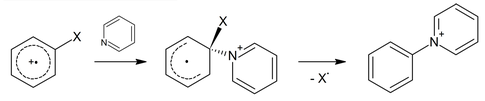
Min.: $\frac{\partial^2 E}{\partial R_i^2} > 0 \quad \forall i$

TS: $\frac{\partial^2 E}{\partial R_j^2} < 0 \quad R_j = RC$

Fig. 2: Example of a PES with a minimum (Min) and a transition state (TS)

Reaction Mechanism for different Dopants

Proposed Mechanism:



Dopant$^+$ [M+Dopant]$^+$ [M+Ph]$^+$

Calculations (without dispersion correction):

- pyridine was chosen the as analyte (Group 1)
- reaction mechanism for each halobenzene (PhF, PhCl, PhBr, PhI)

Results:

- A weak intermediate (IS1) where the lone pair of the nitrogen is attracted to the positive charge (located mostly at C_1) is always observed.
- A transition state (TS1) follows, where pyridine breaks the π-system of the dopant (very low for PhF^+).
- For fluoro- and chlorobenzene a second intermediate (IS2) is found, where C_1 is in a sp^3 hybridization ($[M+Dopant]^+$).
- A simultaneous cleavage of the C_1-X bond with formation of the C_1-N bond is observed for X=Br,I (possibly due to sterical hindrance).
- Subsequent cleavage of the C_1-X bond for X=F,Cl is energetically demanding for F (due to strong C-F bonding) and easy for Cl.
- Overall, the reaction is thermodynamically favorable for Cl, Br, I while it stops at the adduct for F. This is exactly what has been observed in the mass spectra[1].

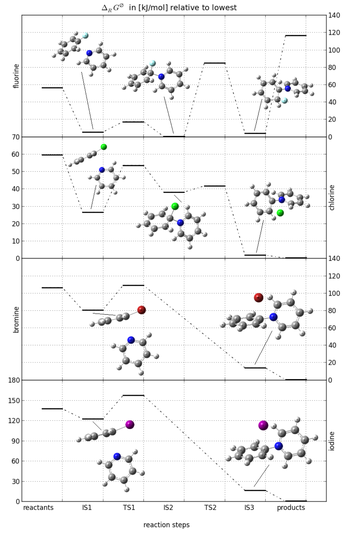


Fig. 3: Gibbs free energy along the reaction of pyridine with each halobenzene[1].

Pyrrole

Question:

- Why is the *ipso*-substitution observed with pyridine but not at all with pyrrole?

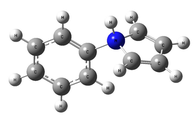
Calculations:

- 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 regarding the C_1-N bond).
- Reaction is highly endergonic since the aromatic system of pyrrole remains destroyed.
- The positive charge is poorly delocalized.

reaction	$\Delta_R G$ [kJ/mol]
pyridine + $PhCl^+$	-59.6
pyrrole + $PhCl^+$	55.8



[Pyrrole + Ph]$^+$

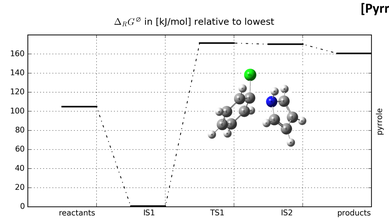


Fig. 4: Gibbs free energy along the reaction of pyrrole with a cholobenzene radical cation.

2-Cyclohexen-1-one / Cyclohexanone

Question:

- In which way is the reaction supported by the double bond in 2-cyclohexen-1-one (Group 2) in comparison to cyclohexanone (Group 3)?

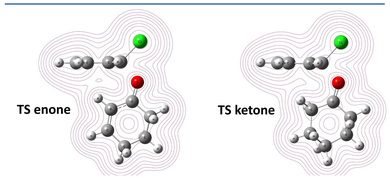
Calculations

- Search for IS and TS according to the mechanism shown to the left.

Results:

- For 2-cyclohexen-1-one, the reaction path is reasonable, although clearly exergonic only for $PhBr^+$ and just slightly for $PhCl^+$.
- TS1 is already high in energy for 2-cyclohexen-1-one (67 kJ/mol rel. to IS1). Without the hydrogen bond stabilization to the phenyl-ring and the delocalization of the positive charge through the resonance stabilization of the enone, TS1 is even more unfavorable for cyclohexanone (~80 kJ/mol rel. to IS1).
- So far, no IS2 has been found for cyclohexanone. Every optimization procedure led back to IS1.
- The stabilization of the TS1/IS2 is the main reason for the difference between the two structurally similar compounds.
- Resonance stabilization also affects the products, where cyclohexanone is ~20 kJ/mol less favorable than 2-cyclohexen-1-one for both, PhCl and PhBr.

reaction	$\Delta_R G$ [kJ/mol] X = Cl	X = Br
enone + PhX^+	-9.2	-44.6
ketone + PhX^+	9.8	-25.6



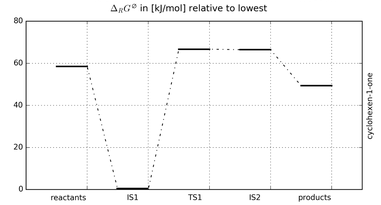


Fig. 5: $\Delta_R G$ along the reaction of 2-cyclohexen-1-one with $PhCl^+$.

Oxazole

Question:

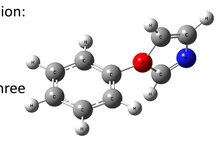
- Which position of the oxazole attacks the halobenzene ion: the oxygen, the nitrogen or the carbon in between?

Calculations:

- Geometry optimization and thermodynamics for the three different products.

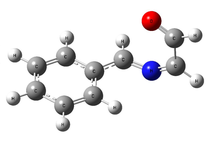
Results:

- O: The two rings are orthogonal (89.8°), hence there is no overlap of the π-systems → unfavorable (strikingly high Gibbs free reaction enthalpy, possibly poor delocalization of the positive charge in the oxazole ring).
- C: The oxazole ring opens so that the carbon remains in a sp^2 configuration. Stabilization of the positive charge (mostly located at benzyl position) through the oxygen in the aldehyde group and the phenyl ring.
- N: Angle between rings is 44.6°. Hence there is an overlap between the π-systems (same in pyridine); positive charge distributed throughout the oxygen/the entire ring.
- Only the attack of the N atom leads to an exergonic reaction.

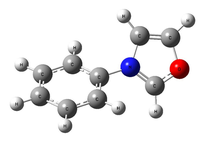


O - product

reaction	$\Delta_R G$ [kJ/mol]
oxazole + $PhCl^+$ (O)	165.9
oxazole + $PhCl^+$ (C)	24.5
oxazole + $PhCl^+$ (N)	-45.0



C - product



N - product

Conclusions

- The calculations support the proposed mechanism of the *ipso*-substitution. For some analyte/dopant combinations, an adduct $[M+Dopant]^+$ is formed (even the global minimum for pyridine + PhF^+), while it is missing for others (pyridine + $PhBr^+$).
- Delocalization of the positive charge through any type of π-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 π-systems in the product (oxazole + $PhCl^+$ works better at C- than at O-position).
- Aromatic N-compounds seem to react most favorably.
- In general, the reaction is favored by increasing size of the halogen.
- Ab initio calculations supported the experimental results (each calculation shown is consistent with the experimental data). They reveal a deeper insight into the fundamental chemistry behind the observed mass spectra.

Outlook

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

Literature

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Acknowledgement

Financial support by **iGenTraX UG (Haan, Germany)** is gratefully acknowledged.