

Thermodynamic and kinetic investigation of proton transfer reactions between amines and solvent clusters

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Introduction

Gas phase matrices of atmospheric pressure ion (API) sources contain solvent molecules in the ppmV to vol% regime. Regardless of the origin of ions, whether from desolvation processes or from bare neutral gas phase molecules, such environments drive pronounced and highly dynamic ion-cluster chemistry. In certain applications this is used by specifically adding solvent molecules to the gas phase. These can gain control over ion properties, such as the charge state or (differential) ion mobility.

Experimental data with Substance P (SP), a small peptide, suggest that gas phase solvent molecules not only cluster around the protonated analyte but, notwithstanding their lower proton affinity (PA), also deprotonate. For example, adding methanol (MeOH) to the gas phase depletes the 3+ charge state forming the 2+ state exclusively. However, acetonitrile (ACN) preserves the 3+ charge state and even the [SP+3H+ACN]³⁺ cluster is observed with relatively soft ion transfer settings.

The PAs of both additives is essentially lower than, e.g., of methylamine (MeNH₂), which is used as the model compound for protonated amine side chains of basic amino acids in this work. Consequently, the proton transfer to a single additive molecule is very unlikely. However, several additive molecules, clustered around the charge, increase the PA and can readily deprotonate the amine.

This contribution theoretically investigates MeOH and ACN as additives (A) with MeNH₂ as the analyte (M) to clarify the mechanism with regard to the characteristic different behavior of those two additives.

The thermodynamic stability of the additive clusters [M+H+nA]⁺ and the pure clusters (A)_nH⁺ is investigated. Due to loosely bound H-bridges, anharmonic effects are accounted for with a newly developed hybrid method.

The potential energy surface (PES) along the proton transfer (PT) paths is also investigated for different cluster species to show possible kinetic effects.

The effect of an adjacent second charge on the PT, as is the case in the experimentally investigated multiply charged SP, is modeled with doubly protonated ethylenediamine.

Computational Details

Software package:

Gaussian09, Revision C.01^[2] for calculations
GaussView 4.1^[3] for visualization
Python scripts for plotting

Machine:

Linux-based computer cluster, 4x16-Core CPUs (6282SE AMD Opteron; Advanced Micro Devices GmbH, Dornach, Germany) and 32x16 GB memory

Methods

Geometry Optimization:

- **B3LYP-D/def2-TZVPP** with empirical dispersion^[1] (**m-level**)
- ultrafine integration grid and tight convergence criteria for SCF and gradient

Thermodynamics:

- Electronic energy E_0 recalculated with **B2PLYP-D/def2-QZVPP** (**h-level**) on (**m-level**)-optimized geometry
- Harmonic frequencies ω_k and equilibrium rotational constants A_e, B_e, C_e obtained on (**m-level**)
- **B3LYP-D/def2-SVP** (**l-level**) optimized geometry was used for anharmonic analysis with a second-order perturbative approach^[2-4] on the same level to obtain vibrational anharmonic constants χ_{kl} , vibro-rotational matrix $(\alpha_k^a, \beta_k^b, \gamma_k^c)$ and centrifugal distortion tensor $\tau_{\alpha\beta\gamma\delta}$
- (**l-level**)-coupling constants were combined with (**m-level**)-harmonics (written with \sim):

$$(1) \nu_k = \tilde{\omega}_k + 2\chi_{kk} + \frac{1}{2}\sum_{l \neq k} \chi_{kl}$$

$$(2) E_{ZPE} = \chi_0 + \frac{1}{2}\sum_k (\tilde{\omega}_k + \frac{1}{2}\chi_{kk} + \frac{1}{2}\sum_{l > k} \chi_{kl})$$

$$(3) A'_0 = \frac{\tilde{A}_0 - \frac{1}{2}\sum_k \alpha_k^a}{A_0} + \frac{1}{4} \frac{(3\tau_{bcbc} - 2\tau_{caca} - 2\tau_{abab})}{\text{centrifugal distortion term}}$$

$$(4) B'_0 = \tilde{B}_e - \frac{1}{2}\sum_k \alpha_k^b + \frac{1}{4}(3\tau_{caca} - 2\tau_{abab} - 2\tau_{dbcb})$$

$$(5) C'_0 = \tilde{C}_e - \frac{1}{2}\sum_k \alpha_k^c + \frac{1}{4}(3\tau_{abab} - 2\tau_{dbcb} - 2\tau_{caca})$$

- Anharmonic constants are not sensitive to level of theory^[5]
- Partition functions are calculated with standard harmonic/rigid expressions but using fundamental frequencies and corrected rotational constants according to simple perturbation theory (SPT)^[6]:

$$(6) Q_{vib} = \frac{\exp(-\frac{E_{ZPE}}{k_B T})}{\prod_k \exp(-\frac{h\nu_k}{k_B T})} \quad (7) Q_{rot} = \frac{1}{\sigma} \left(\frac{k_B T}{hc}\right)^{3/2} \left(\frac{\pi}{A'_0 B'_0 C'_0}\right)^{1/2}$$

PES-Scans:

- Scans of the PES along the proton transfer reaction paths were conducted on (**m-level**)
- The bond distance of the amine nitrogen to the proton was elongated; all other coordinates were allowed to relax
- For each observed transition state (TS) an intrinsic reaction coordinate (IRC)^[7] calculation was performed

Method validation:

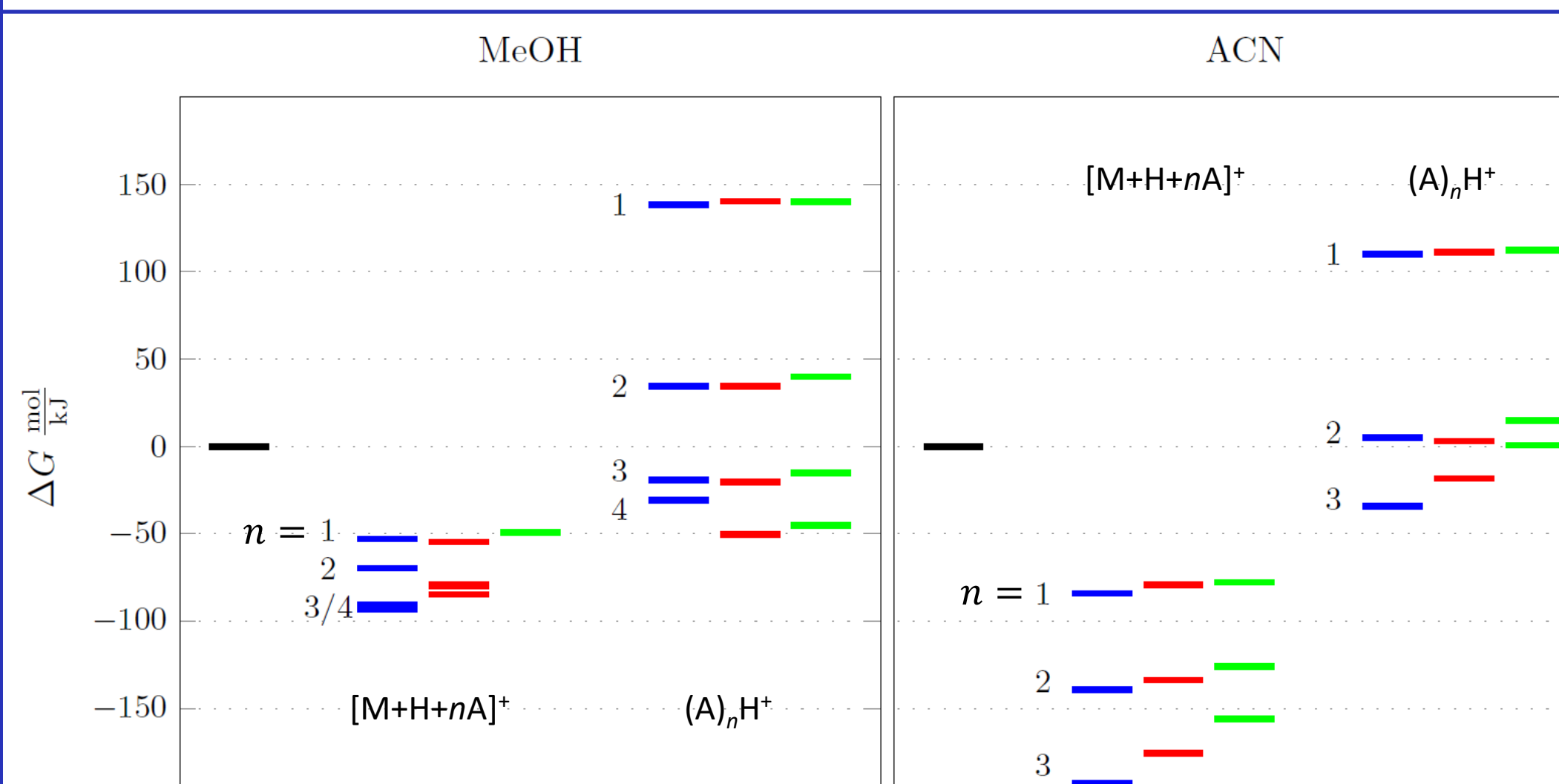
- Proton affinities (PA) and gas phase basicities (GPB) were calculated at 298.15 K and compared with experimental data

Method	MeOH		ACN		MeNH ₂	
	PA	GPB	PA	GPB	PA	GPB
(m-level) harmonic	759.8	729.4	792.9	761.8	904.0	869.6
+ (h-level) energy	754.8	724.4	784.6	753.5	899.2	864.8
+ anharmon. correction	755.4	725.7	784.9	753.9	899.1	864.1
Lit. (exp.) ^[8]	754.3	724.5	779.2	748	899.0	864.5

Thermochemistry of the clusters

Structure of clusters [M+H+nA]⁺ and (A)_nH⁺:

- Homogeneous clusters (A)_nH⁺
 - **MeOH** forms linear H-bond chains
 - Charge formally resides at an oxygen (n odd) or at a proton doubly H-bonded (n even)
 - Charge always distributed over the whole cluster
 - **ACN** can only act as a donor without offering a new binding site
 - (ACN)₃H⁺ thus is only weakly bound (0.44 eV)
 - C₃-symmetric or T-shaped trimer is not stable!
- Additive clusters [M+H+nA]⁺
 - **MeOH** forms linear chains at the protonation site
 - Preformed product clusters (A)_nH⁺
 - Proton stays at the amine
 - **ACN** cannot preform the product clusters
 - Each ACN binds to a different hydrogen



Thermodynamic stability at 298.15 K relative to MeNH₂⁺ + nA (black). Green: exp. Values^[8], Red: (**m-level**)-harmonic + (**h-level**)-energy, Blue: Red+(**l-level**)-anharmonic correction.

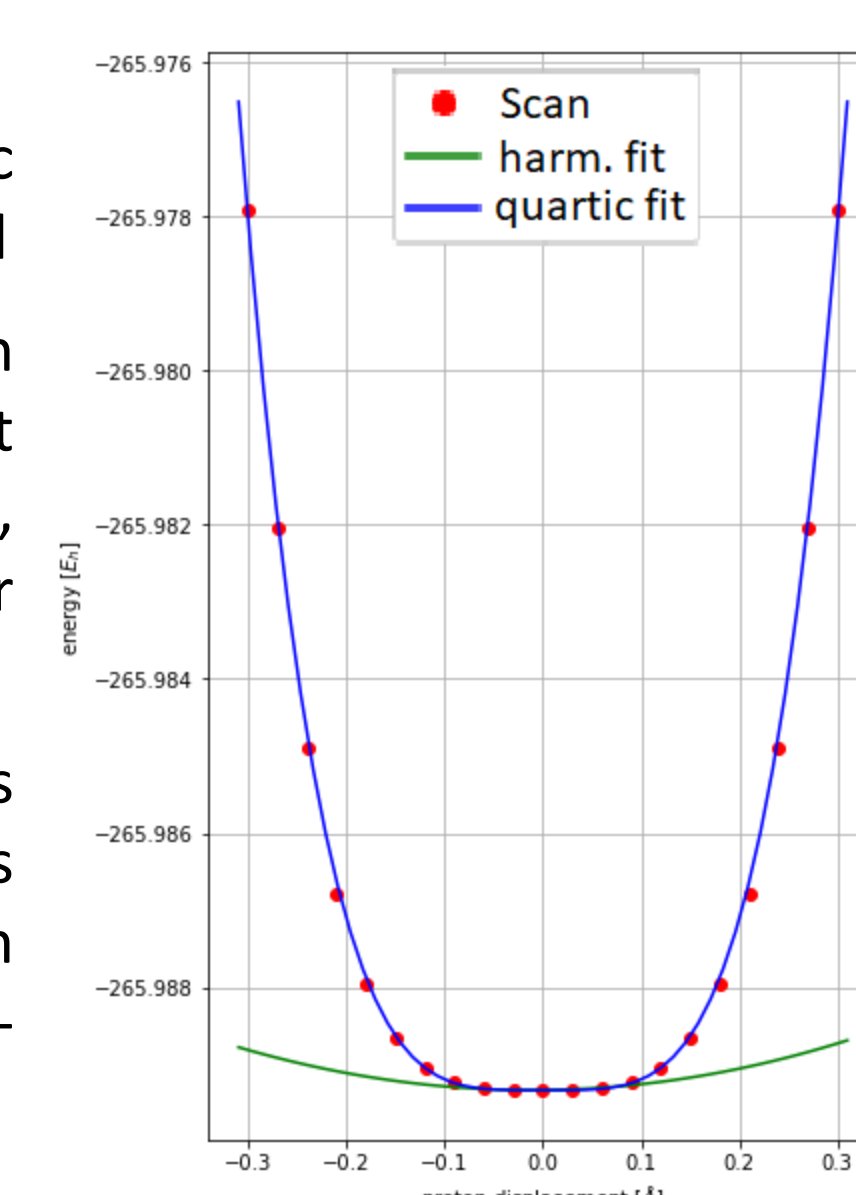
Thermodynamic stability:

- Additive clusters are very stable for ACN (each A binds to another proton), while for MeOH the Gibbs energy is saturated for $n = 4$.
- Enthalpy change to product clusters becomes smaller with n for MeOH but larger for ACN
- Proton Transfer seems feasible for large MeOH clusters but not for ACN
- The anharmonic correction does not seem to improve the accuracy with respect to the experimental values
- Errors are larger for ACN than for MeOH

Problems:

- Internal rotations
 - Especially the ACN clusters show internal rotations (around the C₃ axis) with very low barriers
 - E.g., rotation barrier in (ACN)₂H⁺ is only 3.4 μeV
 - Frequencies of internal rotations can be treated separately from Q_{vib} as free or hindered rotation
 - However, through $\chi_{ir,k}$ they still influence all fundamentals and E_{ZPE} (see eq. (1) and (2))
- Low frequencies
 - Anharmonic correction can sometimes be higher than harmonic frequency leading to negative fundamentals
 - This is observed for low frequencies (often internal rotations)
 - Probably due to inaccuracies in numerical differentiation in anharmonic analysis
 - In this case, only the (**m-level**) harmonics were used

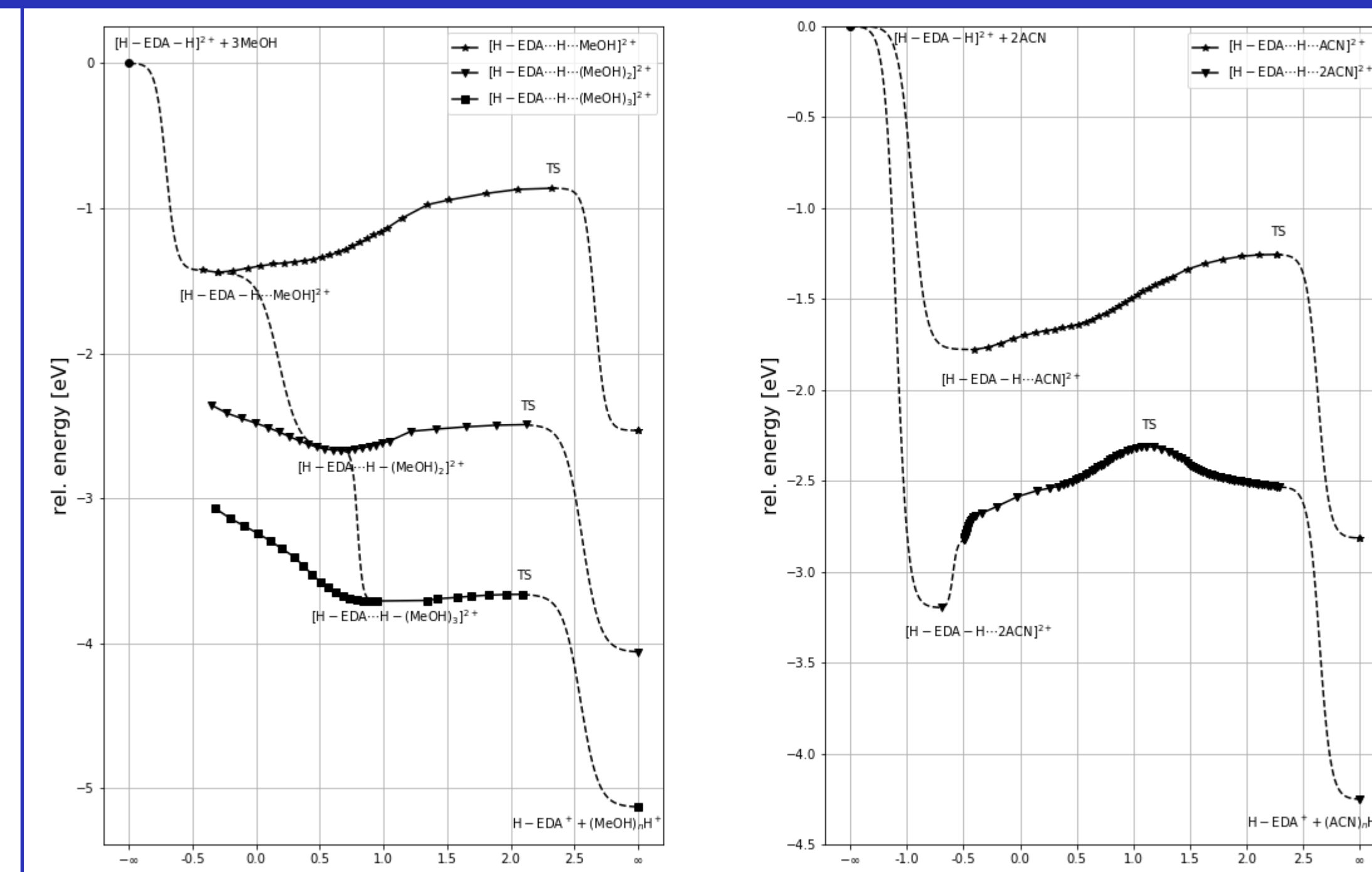
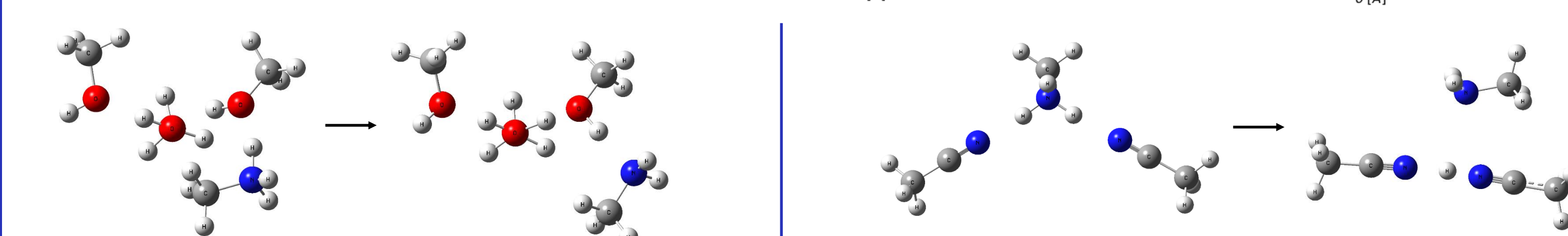
- Highly anharmonic modes were observed
- E.g., proton vibration in (ACN)₂H⁺ is very flat around equilibrium, but rises much faster than harmonic fit
- Anharmonic analysis on (**m-level**) changes the harmonic from 300 cm⁻¹ to a fundamental of 5772 cm⁻¹



PES Scans of proton transfer

PT from MeNH₂:

- Only one minimum for **MeOH** (left)
- PES becomes flatter with increasing n
- 2nd PT shows the charge dilution into the cluster
- From a stable minimum, the loss of one MeOH or PT is equally probable (similar energy and state density)
- However, no clear preference for PT
- For **ACN** (right), TS has to be passed in dimer due to high change in geometry
- PT is very unlikely (high barrier and low state density compared to the loss of one ACN)



PT from doubly protonated ethylenediamine (EDA):

- Introducing a second charge makes the PT for **MeOH** (left) feasible
- The situation for **ACN** (right) is still difficult (barrier is even higher for $n=2$ than for $n=1$) due to the same geometry change

Conclusions

Method:

- Additional (**h-level**) energy improves the thermochemical data (e.g., PA and GPB) compared to the pure (**m-level**) harmonic approach
- Anharmonic corrections merely alter the PA and GPB but largely contribute to the cluster stabilities. However, the hybrid method did not prove to always be superior to the (**m-level**) harmonic with (**h-level**) energy. A reasonable explanation for this finding could be the impact of internal rotations and other low frequency contributions. High anharmonic modes, however, indicate the importance of anharmonicity to be considered in clusters

Cluster chemistry:

- Thermochemical and kinetic analysis support the idea of PT into clusters
- This PT occurs either as a pure gas phase reaction or in nano-sized droplets of the additive
- MeOH and ACN significantly differ in their ability to form hydrogen bond chains. MeOH immediately forms product cluster like structures at the protonation site, whereas ACN is forced to go through considerable geometry changes with high energy barriers
- This effect is pronounced when a second charge is introduced: MeOH dilutes it into the clusters H-bond chain, ACN shows more ligand character

Outlook

- More testing of hybrid method with other compounds (rigid / loosely bound)
- Handling of internal rotations
- Experimental investigation of primary amines (singly and doubly charged) to validate the calculations

Literature

- [1] Grimme, S. (2006): *J. Comp. Chem.*, 27(15), 1787–1799.
- [2] Clabo, D.A., Allen, W.D., Remington, R.B., Yamaguchi, Y., & Schaefer, H.F. (1988): *Chem. Phys.*, 123(2), 187–239.
- [3] Barone, V. (2004): *J. Chem. Phys.*, 120(7), 3059–3065.
- [4] Barone, V. (2005): *J. Chem. Phys.*, 122(1), 14108.
- [5] Peterson, K.A., Feller, D., & Dixon, D.A. (2012): *Theor. Chem. Acc.*, 131(1), 1079.
- [6] Truhlar, D.G., & Isaacson, A.D. (1991): *J. Chem. Phys.*, 94(1), 357–359.
- [7] Fukui, K. (1981): *Accounts of Chemical Research*, 14(12), 363–368
- [8] NIST data base

Acknowledgement

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