QUANTUM CHEMICAL RESEARCH NOTE & COMPUTATIONAL CHEMISTRY

Protonation and Aqueous Solvation Effects on the Thermal Homolytic Decomposition of 2,2'-Azobis(2-amidinopropane) (AZPH / AAPH)

A Comparative Density Functional Theory (DFT) Relaxed Bond-Scission Study

Author: Wolfgang Dorner | **Method:** Unrestricted B3LYP/def2-SVP & ddCOSMO (Water) | **Software:** PySCF & geomeTRIC

ABSTRACT

2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH / V-50; free base abbreviated here as **AZPH**) is a benchmark water-soluble azo initiator widely employed in radical polymerization and free-radical biochemistry. Under physiological and aqueous polymerization conditions, both amidino substituents are protonated, yielding the dicationic species **[AZPH+2H]$^{2+}$**. Using unrestricted Density Functional Theory (**UB3LYP/def2-SVP**) with broken-symmetry singlet diradical initialization and continuum solvation (**ddCOSMO**, ε = 78.39), we investigated the relaxed homolytic C–N bond-scission pathway from the equilibrium C–N distance (1.48 Å) to complete dinitrogen (N_2) extrusion (3.50 Å). Protonation combined with aqueous solvation lowers the electronic dissociation barrier by **15.9 kJ/mol** (from **+165.7 kJ/mol** in the neutral gas-phase free base to **+149.8 kJ/mol** in aqueous [AZPH+2H]$^{2+}$) and shifts the transition-state-like energy maximum to an earlier C–N bond extension (2.30 Å vs. 2.50 Å), in full agreement with the Hammond postulate.

1. Introduction & Chemical Background

Symmetric aliphatic azo compounds (R–N=N–R) serve as clean, temperature-controlled sources of carbon-centered free radicals via unimolecular thermal extrusion of molecular nitrogen (N_2) [1, 2]. While oil-soluble initiators such as azobisisobutyronitrile (AIBN) dominate organic media, **2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH / V-50)** is the prototypical hydrophilic radical initiator for aqueous emulsion polymerizations and biological lipid peroxidation assays [2, 3].

Because the amidino group (–C(=NH)NH_2) is strongly basic (pK_a ≈ 11–12), AAPH exists almost exclusively as the doubly protonated dication **[AZPH+2H]$^{2+}$** in neutral and acidic aqueous solution. Understanding how dual protonation and polar water solvation reshape the potential energy surface (PES) of C–N bond homolysis is critical for predicting initiation rates, radical stability, and cage-recombination behavior.

2. Computational Methodology

All quantum chemical calculations were performed using the open-source Python-based electronic structure framework **PySCF** [4, 5] coupled with the **geomeTRIC** internal-coordinate geometry optimizer [6].

- **Electronic Structure Level:** Hybrid Density Functional Theory employing the **B3LYP** exchange-correlation functional [7, 8] with the polarized split-valence Ahlrichs **def2-SVP** basis set [9].
- **Diradical Treatment (Broken-Symmetry DFT):** Homolytic C–N cleavage generates a singlet diradical pair (an amidinopropyl radical and an incipient diazenyl/carbon radical fragment). To describe spin-unpairing smoothly along the dissociation coordinate without artificial ionic contamination, unrestricted Kohn–Sham (**UKS** / **UB3LYP**) calculations with broken-symmetry (α/β HOMO–LUMO) mixing were applied [10–12].
- **Aqueous Solvation Model:** Bulk electrostatic solvation in water (ε = 78.39) was incorporated self-consistently via the domain-decomposition Conductor-like Screening Model (**ddCOSMO**) [13, 14].
- **Relaxed Potential Energy Surface (PES) Scan:** Starting from the fully optimized equilibrium geometries ($r_{C–N}$ ≈ 1.48 Å), one C–N bond was elongated stepwise across 16 constrained grid points up to 3.50 Å, relaxing all remaining internal degrees of freedom at each step.

3. Results & Comparative Energetics

Both systems exhibit a smooth, endothermic C–N bond dissociation curve leading to clean extrusion of a linear N_2 molecule ($\Delta r_{N\equiv N}$ ≈ 1.10 Å at 3.50 Å) and two resonance-stabilized 2-amidinoprop-2-yl radicals. However, protonation and aqueous solvation induce pronounced quantitative and structural shifts along the reaction coordinate.

Property / Reaction Parameter	Neutral Free Base (AZPH, Gas Phase)	Dication ($[AZPH+2H]^{2+}$, Aqueous ddCOSMO)	Net Solvation & Protonation Effect
Total Molecular Charge / Multiplicity	0 / Singlet (Broken-Symmetry UKS)	+2 / Singlet (Broken-Symmetry UKS)	Dual amidino protonation (–$C(NH_2)_2^+$)
Environment / Dielectric Constant	Vacuum (ε = 1.00)	Water, ddCOSMO (ε = 78.39)	Strong polar continuum stabilization
Equilibrium C–N Bond Length (r_{eq})	1.48 Å	1.48 Å	Unchanged ground-state C–N linkage
Peak Energy Barrier ($\Delta E^{\ddagger}_{elec}$)	**+165.7 kJ/mol**	**+149.8 kJ/mol**	**–15.9 kJ/mol** barrier reduction
C–N Distance at Energy Maximum	2.50 Å	2.30 Å	**–0.20 Å** earlier transition state
Reaction Energy at 3.50 Å ($\Delta E_{3.50}$)	+154.2 kJ/mol	+136.5 kJ/mol	**–17.7 kJ/mol** product stabilization

Key Mechanistic Conclusions:

- **Electrostatic & Radical Stabilization:** In $[AZPH+2H]^{2+}$, the positively charged amidinium moieties ($–C(NH_2)_2^+$) experience strong hydration shells in ddCOSMO water and delocalize spin density more effectively upon planarization of the α-carbon radical center, lowering the activation barrier by **15.9 kJ/mol**.
- **Hammond Postulate Manifestation:** Because the radical products are thermodynamically stabilized by 17.7 kJ/mol in aqueous solution, the transition-state-like energy maximum shifts toward a shorter C–N bond length (**2.30 Å** instead of **2.50 Å**) [15].
- **Stepwise vs. Concerted Cleavage:** Along the single-bond relaxed scan, the second C–N bond elongates cooperatively once the first C–N distance exceeds 2.30 Å, confirming an asynchronous concerted-like N_2 extrusion pathway consistent with prior DFT studies on aliphatic azo initiators [16, 17].

4. Computational Environment & Reproducibility

All geometry optimizations, relaxed PES scans, and trajectory post-processing routines were executed locally on a dedicated workstation without cloud dependencies:

- **Hardware Architecture:** Apple Mac Studio (Apple M2 Ultra, 24-core CPU, 64 GB unified memory, external 8 TB NVMe SSD storage).
- **Visualization & Trajectory Smoothing:** 16-frame DFT relaxed trajectories were linearly interpolated (4× sub-stepping plus 20-frame reactant/product dwell buffers) into 100-frame smooth animations, rendered in **Avogadro 2** [18] with dynamic bond perception and encoded via **FFmpeg** (H.264/MP4).

5. References

1. Engel, P. S. Mechanism of the thermal and photochemical decomposition of azoalkanes. *Chem. Rev.* **1980**, *80* (2), 99–150.
2. Niki, E. Free radical initiators as source of water- or lipid-soluble peroxyl radicals. *Methods Enzymol.* **1990**, *186*, 100–108.
3. Werber, J.; Wang, Y. J.; Milligan, M.; Li, X.; Ji, J. A. Analysis of 2,2'-azobis(2-amidinopropane) dihydrochloride degradation and hydrolysis in aqueous solutions. *J. Pharm. Sci.* **2011**, *100* (8), 3307–3315.
4. Sun, Q.; Berkelbach, T. C.; Blunt, N. S.; Booth, G. H.; Guo, S.; Li, Z.; Liu, J.; McClain, J. D.; Sayfutyarova, E. R.; Sharma, S.; Wouters, S.; Chan, G. K.-L. PySCF: the Python-based simulations of chemistry framework. *WIREs Comput. Mol. Sci.* **2018**, *8* (1), e1340.
5. Sun, Q. et al. Recent developments in the PySCF program package. *J. Chem. Phys.* **2020**, *153* (2), 024109.
6. Wang, L.-P.; Song, C. Geometry optimization made simple with translation and rotation coordinates. *J. Chem. Phys.* **2016**, *144* (21), 214108.
7. Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98* (7), 5648–5652.
8. Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* **1988**, *37* (2), 785–789.
9. Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7* (18), 3297–3305.

10. Noodleman, L. Valence bond description of antiferromagnetic coupling in transition metal dimers. *J. Chem. Phys.* **1981**, *74* (10), 5737–5743.
11. Yamaguchi, K.; Jensen, F.; Dorigo, A.; Houk, K. N. A spin correction procedure for unrestricted Hartree-Fock and Møller-Plesset wavefunctions for singlet diradicals and polyradicals. *Chem. Phys. Lett.* **1988**, *149* (5–6), 537–542.
12. Neese, F. Prediction of molecular properties and molecular spectroscopy with density functional theory: From fundamental theory to exchange-coupling. *Coord. Chem. Rev.* **2009**, *253* (5–6), 526–563.
13. Cancès, E.; Maday, Y.; Stamm, B. Domain decomposition for implicit solvation models. *J. Chem. Phys.* **2013**, *139* (5), 054111.
14. Lipparini, F.; Scalmani, G.; Lagardère, L.; Stamm, B.; Cancès, E.; Maday, Y.; Piquemal, J.-P.; Frisch, M. J.; Mennucci, B. Quantum, classical, and hybrid QM/MM calculations in solution: General implementation of the ddCOSMO linear scaling strategy. *J. Chem. Phys.* **2014**, *141* (18), 184108.
15. Hammond, G. S. A correlation of reaction rates. *J. Am. Chem. Soc.* **1955**, *77* (2), 334–338.
16. Liu, Y.; Shu, Y. Theoretical study on the thermal decomposition mechanism of azobisisobutyronitrile (AIBN). *J. Mol. Struct.: THEOCHEM* **2009**, *901* (1–3), 104–109.
17. Noble, B. B.; Coote, M. L. First principles modelling of free-radical polymerisation kinetics. *Int. Rev. Phys. Chem.* **2013**, *32* (3), 467–513.
18. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: an advanced semantic chemical editor, visualization, and analysis platform. *J. Cheminform.* **2012**, *4*, 17.