

**SEQUENCE-DEPENDENT THERMODYNAMIC STABILITY AND
QUANTUM-CHEMICAL REACTIVITY DESCRIPTORS OF ADENINE-
INITIATED DNA TRINUCLEOTIDES: A SEMI-EMPIRICAL
AM1/MOPAC 2016 INVESTIGATION**

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ABSTRACT

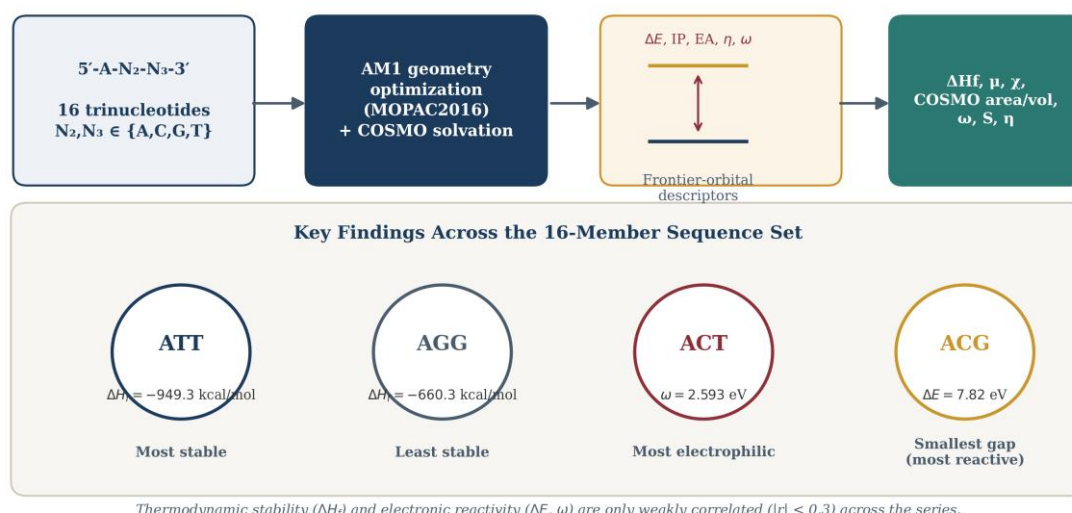
The sequence-dependent electronic structure of DNA oligomers underlies key biological phenomena, including oxidative lesion formation, radical whole transport, and mutational hot-spot behaviour. In this work, the complete set of sixteen adenine-initiated DNA trinucleotides (5'-A-N₂-N₃-3'; N₂, N₃ ∈ {A, C, G, T}) was investigated using the semi-empirical AM1 Hamiltonian implemented in MOPAC2016 (Version 23.2.5W), with implicit aqueous solvation described by the Conductor-like Screening Model (COSMO). Fully optimized geometries were used to extract heats of formation (ΔH_f), dipole moments, frontier molecular orbital (E_{HOMO}/E_{LUMO}) energies, COSMO solvent-accessible surface areas and volumes, and molecular weights. Koopmans'-theorem-derived conceptual density functional theory descriptors — ionization potential, electron affinity, electronegativity, chemical hardness, softness,

chemical potential, and the global electrophilicity index (ω) — were subsequently computed for every sequence. The most thermodynamically stable trinucleotide was ATT ($\Delta H_f = -949.31 \text{ kcal mol}^{-1}$), whereas AGG was the least stable ($\Delta H_f = -660.31 \text{ kcal mol}^{-1}$). Dipole moments spanned a sixteen-fold range (1.55–18.08 D), with the purine-rich AGC sequence showing the largest polarity. The HOMO–LUMO gap varied from 7.82 eV (ACG) to 8.60 eV (ATA), and, as required by their shared definition, tracked the chemical hardness with a Pearson correlation coefficient of $r = 1.00$. The pyrimidine-terminated ACT sequence

displayed the highest electrophilicity index ($\omega = 2.593$ eV), identifying it as the most electrophilic member of the series, while AAC was the least electrophilic ($\omega = 2.334$ eV). Thermodynamic stability (ΔH_f) and electronic reactivity indices were only weakly correlated ($|r| < 0.3$), indicating that sequence-dependent thermodynamic and frontier-orbital reactivity behave as largely independent structural descriptors. These results provide a systematic, internally consistent quantum-chemical reference set for adenine-initiated trinucleotide fragments and offer mechanistic groundwork for rationalizing sequence-specific DNA reactivity, oxidative susceptibility, and future ligand/mutagen-interaction studies.

Graphical Abstract

Sequence-Dependent Reactivity of Adenine-Initiated DNA Trinucleotides (AM1/COSMO, MOPAC2016)



Graphical Abstract: Workflow (sequence library → AM1/COSMO optimization → frontier-orbital descriptors → key properties) and headline findings for the sixteen adenine-initiated DNA trinucleotides.

KEYWORDS: DNA trinucleotides, adenine, AM1 semi-empirical method, MOPAC2016, COSMO solvation, HOMO–LUMO gap, conceptual DFT, electrophilicity index.

INTRODUCTION

Deoxyribonucleic acid (DNA) is not an electronically inert information carrier: the π -stacked array of nucleobases supports charge (whole) migration, and the local electronic structure of a given base or short sequence context strongly modulates its susceptibility to oxidative attack, alkylation, and other chemical transformations. Guanine-rich runs are preferentially oxidized in double-stranded DNA because the highest occupied molecular orbital (HOMO) — and hence the site of lowest ionization potential — is localized on 5'-flanking guanines within GG

and GGG steps, a phenomenon with direct relevance to mutagenesis, carcinogenesis, and cellular aging.^[1,2] More broadly, DNA charge transport chemistry has established that hole and electron migration along the duplex is exquisitely sequence-dependent, with implications ranging from DNA-mediated redox signalling to damage-detection strategies.^[3]

Quantum-chemical descriptors offer a natural, physically transparent language for quantifying this sequence dependence. Within Kohn–Sham/Koopmans-theorem-based conceptual density functional theory (DFT), the frontier orbital energies of a molecule can be mapped onto operational estimates of ionization potential (IP) and electron affinity (EA), from which global reactivity indices — electronegativity (χ), chemical hardness (η), softness (S), chemical potential (μ), and the electrophilicity index (ω) introduced by Parr, von Szentpály and Liu — are derived.^[4,5,6] These indices have been used extensively to rank the relative electrophilic or nucleophilic character of organic and biomolecular species and correlate well with experimentally observed reactivity trends across diverse chemical families.

Ab initio and density-functional treatments of nucleobases, base pairs, and base-pair steps have clarified how stacking geometry and hydrogen-bonding pattern influence frontier orbital energies and HOMO–LUMO gaps in dinucleotide steps:^[7,9] however, a systematic, internally consistent survey spanning full trinucleotide sequence space — the natural unit of codon-level and short-repeat biology — is comparatively scarce, in part because higher-level ab initio or DFT geometry optimizations of even small oligonucleotide fragments remain computationally demanding. The semi-empirical AM1 (Austin Model 1) Hamiltonian of Dewar and co-workers,^[10] implemented in the MOPAC family of programs,^[11,12,13] offers a pragmatic compromise: at a small fraction of the cost of DFT, AM1 reproduces heats of formation, dipole moments, and frontier orbital trends for organic and biomolecular systems with an accuracy sufficient for comparative, sequence-scanning studies, and it has a long history of application to nucleic acid components.

In this study, systematically compute and analyse the thermodynamic and quantum-chemical reactivity landscape of the sixteen possible adenine-initiated DNA trinucleotides (5'-A-N2-N3-3'), covering every combination of the second and third bases, in continuous of research work.^[14] Using AM1 geometry optimization in MOPAC2016 together with COSMO implicit aqueous solvation, it is reported heats of formation, dipole moments, frontier orbital ($E_{\text{HOMO}}/E_{\text{LUMO}}$) energies, COSMO surface areas and volumes, and the full set of Koopmans-

theorem-derived global reactivity descriptors for each sequence. We further examine the correlations among these descriptors to establish which properties are structurally coupled (e.g., hardness and $E_{\text{HOMO}}-E_{\text{LUMO}}$ gap, by definition) and which vary independently (e.g., thermodynamic stability versus electronic reactivity), and discussed the results in the context of known sequence-dependent DNA oxidation and charge-transport chemistry.

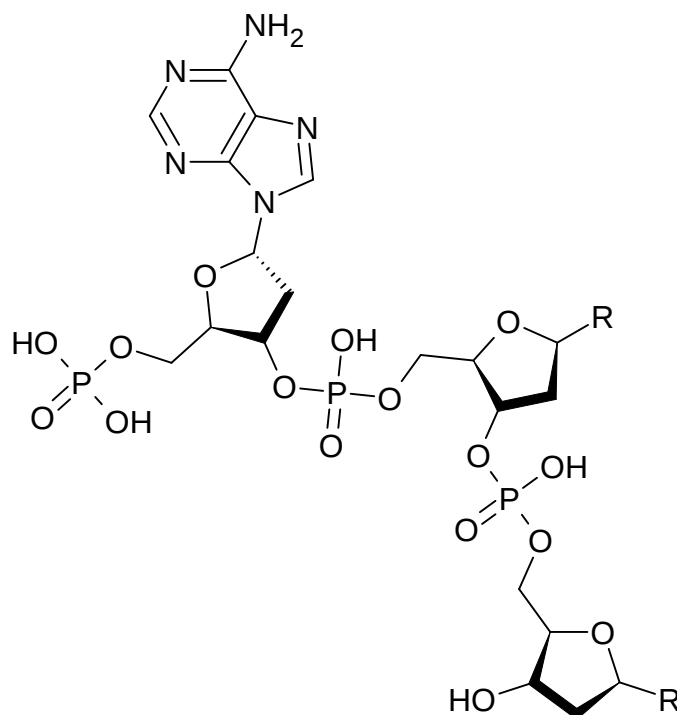


Figure - 1: - Adenine-initiated DNA Trinucleotides
R = Adenine, Guanine, Cytosine, Thymine

Computational Methodology

Sequence library and structure construction

Sixteen single-stranded DNA trinucleotides of the general form 5'-A-N2-N3-3' were constructed, with adenine fixed at the 5'-terminal position and N2, N3 independently sampled over the four canonical bases {A, C, G, T}, giving complete coverage of the $4 \times 4 = 16$ second/third-position sequence space (AAA, ACA, AGA, ATA, AAC, ACC, AGC, ATC, AAG, ACG, AGG, ATG, AAT, ACT, AGT, ATT). Each trinucleotide was built with standard Watson-Crick base geometry and a 3', 5'-phosphodiester-linked deoxyribose backbone bearing a single terminal negative charge convention consistent with the neutral closed-shell singlet electronic configuration used throughout (Figure – 1).

Geometry optimization (AM1/MOPAC2016)

Full geometry optimization, without symmetry constraint, was performed for every trinucleotide at the semi-empirical AM1 level of theory, as implemented in MOPAC2016 (Version 23.2.5W; Stewart Computational Chemistry).^[13] AM1 is a neglect-of-diatomic-differential-overlap (NDDO) Hamiltonian that substantially improved on MNDO in reproducing hydrogen-bonded and stacked systems, which makes it a suitable, computationally tractable choice for base-paired and base-stacked nucleic acid fragments. Each structure was optimized to a gradient norm consistent with the MOPAC default EF (eigenvector-following) convergence criteria, in the singlet ground electronic state with zero net spin. From the converged wave function, MOPAC reports the heat of formation (ΔH_f), the dipole moment, and the energies of all molecular orbitals, from which the E_{HOMO} and E_{LUMO} energies were extracted.

Implicit solvation (COSMO)

To approximate the polar, aqueous cellular environment of DNA, the Conductor-like Screening Model (COSMO) of Klamt and Schüürmann.^[15] was applied during geometry optimization. COSMO represents the solvent as a dielectric continuum enclosing the solute cavity and self-consistently computes the induced surface polarization charge; in addition to its stabilizing effect on ΔH_f and the electronic structure, COSMO calculations provide the solvent-accessible cavity surface area and cavity volume for each optimized geometry, which are reported alongside the electronic descriptors.

Derived quantum-chemical reactivity descriptors

Vertical ionization potential and electron affinity were approximated from the frontier orbital energies via Koopmans' theorem^[16]:

$$IP \approx -E_{HOMO} \quad EA \approx -E_{LUMO}$$

From IP and EA, the following global conceptual-DFT reactivity descriptors were calculated using the standard Parr–Pearson formalism:^[4,5,6]

$$\text{Electronegativity: } \chi = (IP + EA) / 2$$

$$\text{Chemical hardness: } \eta = (IP - EA) / 2$$

$$\text{Softness: } S = 1 / \eta$$

$$\text{Chemical potential: } \mu = -\chi$$

$$\text{Electrophilicity index: } \omega = \mu^2 / 2\eta$$

The electrophilicity index ω , introduced by Parr, von Szentpály and Liu^[6], quantifies the propensity of a species to accept electron density from the environment and has been widely

used to rank relative electrophilic reactivity across series of related molecules. The frontier-orbital scheme and the relationships among these descriptors are summarized schematically in Figure - 2.

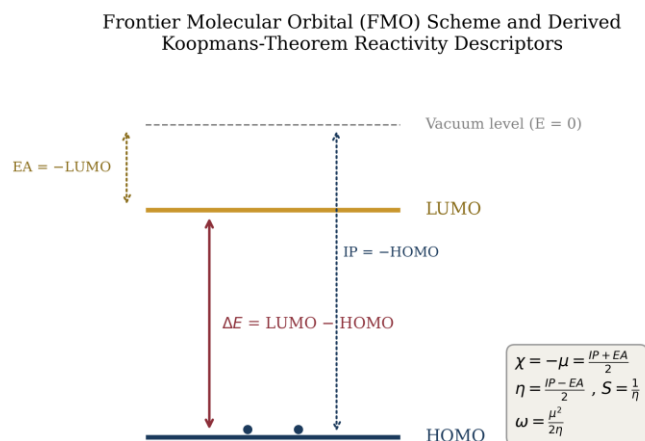


Figure 2: Schematic frontier molecular orbital (FMO) diagram illustrating the E_{HOMO} – E_{LUMO} gap (ΔE) and the Koopmans-theorem relationships used to derive ionization potential (IP), electron affinity (EA), electronegativity (χ), chemical hardness (η), softness (S), and the electrophilicity index (ω) reported in this study.

Data handling and statistical analysis

All computed properties were compiled into two data sets (Tables - 1 and - 2). Descriptive statistics and pairwise Pearson correlation coefficients among descriptors were computed in Python (pandas, NumPy). Bar-chart and heat-map visualizations were generated with Matplotlib. No experimental data were used; all reported values are computed quantities.

RESULTS AND DISCUSSION

Thermodynamic properties

Table - 1 lists the AM1/COSMO heat of formation (ΔH_f), dipole moment, E_{HOMO} and E_{LUMO} energies, COSMO surface area and volume, and molecular weight for all sixteen adenine-initiated trinucleotides. Across the series, ΔH_f ranges from $-949.31 \text{ kcal mol}^{-1}$ (ATT) to $-660.31 \text{ kcal mol}^{-1}$ (AGG), a spread of $289.0 \text{ kcal mol}^{-1}$ (mean = $-787.5 \pm 89.3 \text{ kcal mol}^{-1}$), indicating that thermodynamic stability is highly sensitive to the identity of the second and third bases even though the first (adenine) position and the backbone connectivity are held constant. The four most stable sequences are all pyrimidine-terminated (ATT, ATC, ACT,

AGT), whereas the least stable sequences are purine-rich (AGG, ACA, AAA, AGA), consistent with the generally lower stacking/formation enthalpy contribution of thymine- and cytosine-terminated steps relative to bulkier purine-purine arrangements in this semi-empirical treatment.

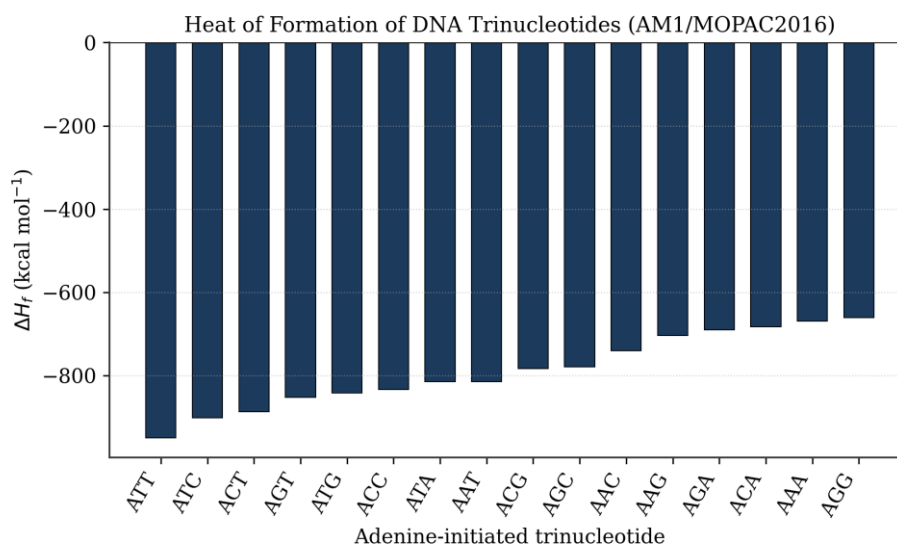


Figure 3: Heat of formation (ΔH_f) of the sixteen adenine-initiated DNA trinucleotides, ranked from most (ATT) to least (AGG) thermodynamically stable.

Dipole moment and molecular polarity

Ground-state dipole moments vary markedly across the series, from 1.554 D (AAT) to 18.082 D (AGC) — more than an order of magnitude — reflecting the strong dependence of overall charge asymmetry on base sequence and backbone conformation. The unusually large dipole moment of AGC suggests a pronounced separation of the ring-nitrogen/carbonyl electron density from the phosphate backbone in its optimized geometry, while the near-cancellation of local bond dipoles in AAT gives it the most electrically symmetric ground state of the set.

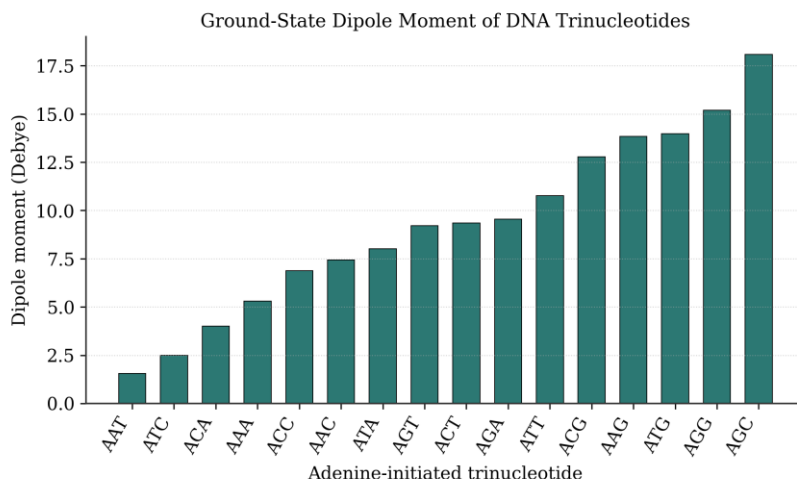


Figure 4: Ground-state dipole moment (Debye) of the sixteen adenine-initiated DNA trinucleotides, ranked from lowest (AAT) to highest (AGC).

Table 1: Thermodynamic and molecular properties of adenine-initiated DNA trinucleotides computed at the AM1method using MOPAC2016 (Version 23.2.5W).

Adenine-initiated DNA Tri-Nucleotides	ΔH_f (Kcal/mol)	Dipole D	HOMO eV	LUMO eV	Cosmo Area (sq ang) ($\text{\AA}^2$)	Cosmo volume (cu ang) ($\text{\AA}^3$)	Mol wt
AAA	-669.0796	5.301	-8.778	-0.272	711.88	1000.86	957.6424
ACA	-683.0295	4.007	-8.649	-0.358	621.02	968.35	933.6174
AGA	-690.0612	9.542	-8.457	-0.486	714.28	1002.84	973.6418
ATA	-814.6292	8.020	-8.862	-0.266	737.69	977.62	948.6290
AAC	-740.2721	7.448	-8.731	-0.196	747.03	956.72	933.6174
ACC	-833.1261	6.874	-8.885	-0.346	673.38	936.17	909.5924
AGC	-779.1867	18.082	-8.644	-0.380	775.50	955.35	949.6168
ATC	-900.9260	2.496	-8.802	-0.345	695.38	945.72	924.6040
AAG	-703.4005	13.845	-8.498	-0.270	769.75	977.71	973.6418
ACG	-782.8181	12.777	-8.214	-0.391	660.28	1001.36	949.6168
AGG	-660.3089	15.200	-8.868	-0.382	704.71	988.65	989.6412
ATG	-841.6778	13.966	-8.665	-0.381	737.74	982.90	964.6284
AAT	-814.0369	1.554	-8.673	-0.296	766.97	976.03	948.6290
ACT	-887.0739	9.342	-8.916	-0.453	716.08	951.28	924.6040
AGT	-851.7904	9.215	-8.466	-0.531	786.02	970.24	964.6284
ATT	-949.3112	10.773	-8.549	-0.352	691.38	973.53	939.6156

Frontier molecular orbital energies

E_{HOMO} energies span a relatively narrow window (-8.916 to -8.214 eV), while E_{LUMO} energies range from -0.531 to -0.196 eV (Table 1; Figure - 5). The deepest E_{HOMO} (most negative, ACT, -8.916 eV) implies the highest vertical ionization potential and, by extension, the lowest intrinsic susceptibility to one-electron oxidation among the series under the

Koopmans approximation, whereas the shallowest E_{HOMO} (ACG, -8.214 eV) marks the sequence most easily ionized. This trend is consistent with the general principle, established for guanine-rich DNA steps, that the site (and sequence context) of the highest-lying occupied orbital determines the kinetically preferred locus of oxidative hole formation.^[1,2] although the present series contains no guanine at the 5' position, the same frontier-orbital logic governs relative oxidizability among adenine-led trinucleotide contexts.

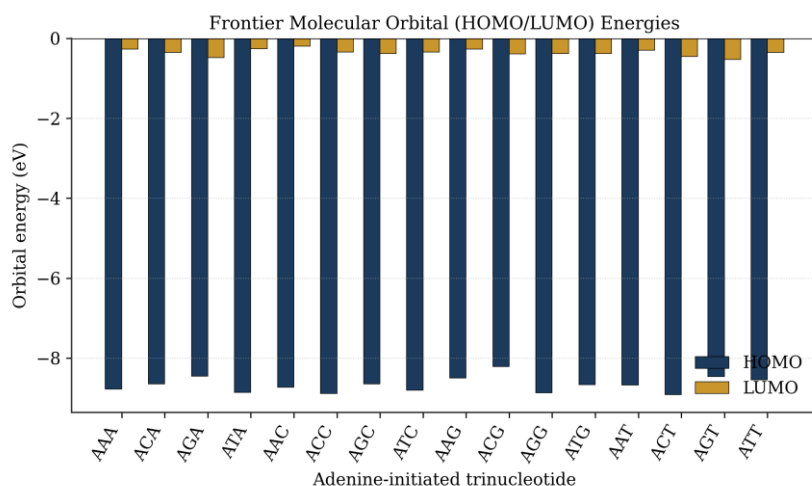


Figure 5: Highest occupied (E_{HOMO}) and lowest unoccupied (E_{LUMO}) molecular orbital energies for the sixteen adenine-initiated DNA trinucleotides.

Global reactivity descriptors: gap, hardness, softness and electrophilicity

Table 2 reports the Koopmans-theorem-derived reactivity descriptors. The $E_{\text{HOMO}}-E_{\text{LUMO}}$ gap (ΔE) ranges from 7.823 eV (ACG) to 8.596 eV (ATA); because $\eta = \Delta E/2$ by construction, the chemical hardness necessarily tracks the gap exactly (Pearson $r = 1.00$ in the present data set; Table - 2), and the corresponding softness ($S = 1/\eta$) is anti-correlated with both. The electrophilicity index ω , which combines electronegativity and hardness, identifies ACT as the most electrophilic sequence ($\omega = 2.593$ eV) and AAC as the least ($\omega = 2.334$ eV). Notably, ACT simultaneously has the deepest E_{HOMO} (lowest IP-implied oxidizability) and the highest ω , illustrating that a species can be simultaneously resistant to oxidation and comparatively electrophilic — hardness and electrophilicity are related but non-identical axes of reactivity, since ω also depends strongly on the electron affinity (E_{LUMO}) side of the frontier gap, where ACT has the second-lowest E_{LUMO} energy (-0.453 eV) in the series.

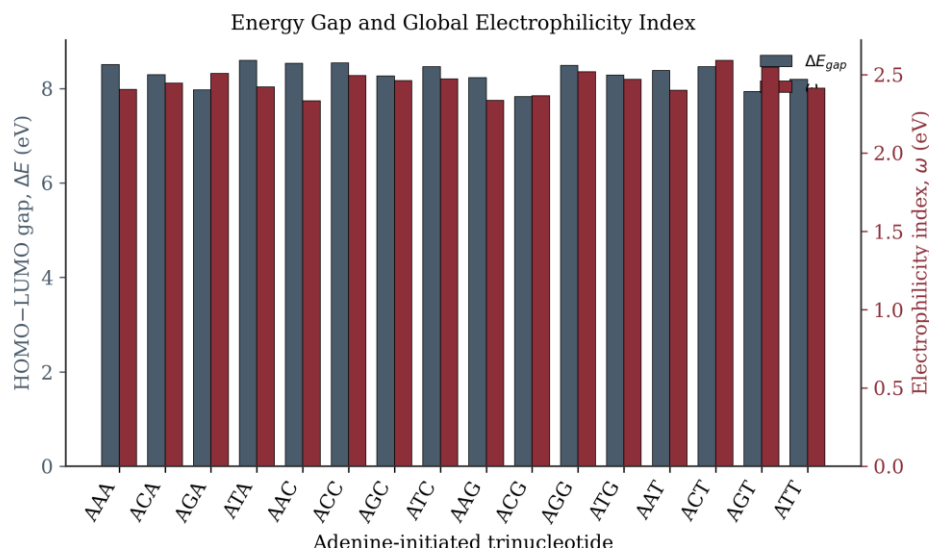


Figure 6: $E_{\text{HOMO}}-E_{\text{LUMO}}$ energy gap (ΔE , left axis) and global electrophilicity index (ω , right axis) for the sixteen adenine-initiated DNA trinucleotides.

Table 2: Frontier orbital energies and Koopmans-theorem-derived conceptual DFT descriptors— $E_{\text{HOMO}}-E_{\text{LUMO}}$ gap (ΔE), ionization potential (IP), electron affinity (EA), electronegativity (χ), chemical hardness (η), softness (S), chemical potential (μ), and electrophilicity index (ω) — for adenine-initiated DNA trinucleotides.

Adenine-initiated DNA Tri-Nucleotides	HOMO eV	LUMO eV	ΔE eV	IP eV	EA eV	EN eV (χ)	Global Hardness eV(η)	Softness (S)	Chem Pot (μ)	Electrophilicity Index (ω)
AAA	-8.778	-0.272	8.506	8.778	0.272	4.525	4.253	1.032	-4.525	2.407
ACA	-8.649	-0.358	8.291	8.649	0.358	4.504	4.146	1.043	-4.504	2.446
AGA	-8.457	-0.486	7.971	8.457	0.486	4.472	3.986	1.061	-4.472	2.508
ATA	-8.862	-0.266	8.596	8.862	0.266	4.564	4.298	1.031	-4.564	2.423
AAC	-8.731	-0.196	8.535	8.731	0.196	4.464	4.268	1.023	-4.464	2.334
ACC	-8.885	-0.346	8.539	8.885	0.346	4.616	4.270	1.041	-4.616	2.495
AGC	-8.644	-0.38	8.264	8.644	0.380	4.512	4.132	1.046	-4.512	2.463
ATC	-8.802	-0.345	8.457	8.802	0.345	4.574	4.229	1.041	-4.574	2.473
AAG	-8.498	-0.27	8.228	8.498	0.270	4.384	4.114	1.033	-4.384	2.336
ACG	-8.214	-0.391	7.823	8.214	0.391	4.303	3.912	1.050	-4.303	2.366
AGG	-8.868	-0.382	8.486	8.868	0.382	4.625	4.243	1.045	-4.625	2.521
ATG	-8.665	-0.381	8.284	8.665	0.381	4.523	4.142	1.046	-4.523	2.470
AAT	-8.673	-0.296	8.377	8.673	0.296	4.485	4.189	1.035	-4.485	2.401
ACT	-8.916	-0.453	8.463	8.916	0.453	4.685	4.232	1.054	-4.685	2.593
AGT	-8.466	-0.531	7.935	8.466	0.531	4.499	3.968	1.067	-4.499	2.550
ATT	-8.549	-0.352	8.197	8.549	0.352	4.451	4.099	1.043	-4.451	2.416

Correlation analysis

Pairwise Pearson correlations among the principal descriptors are summarized in Figure - 7. As expected from their algebraic definitions, ΔE , η are perfectly correlated ($r = 1.00$), and softness is strongly anti-correlated with both ($r \approx -0.69$). Electronegativity χ is very strongly anti-correlated with the chemical potential μ ($r = -1.00$, since $\mu = -\chi$ by definition) and moderately correlated with ω ($r = 0.73$). In marked contrast, the thermodynamic descriptor ΔH_f shows only weak correlation with every electronic reactivity index examined ($|r| \leq 0.32$ in all cases, including the gap, hardness, dipole moment and ω), indicating that, within this series, the enthalpy stability of a trinucleotide and its intrinsic electronic reactivity are governed by largely independent structural factors — most plausibly backbone/base-stacking geometry for the former and frontier π -orbital topology for the latter.

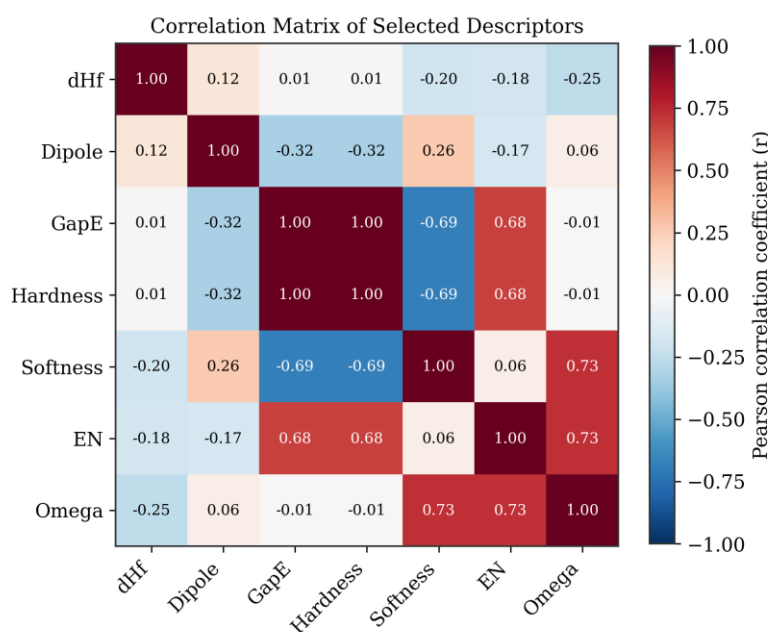


Figure 7: Pearson correlation matrix among heat of formation (ΔH_f), dipole moment, $E_{\text{HOMO}}-E_{\text{LUMO}}$ gap (ΔE), chemical hardness (η), softness (S), electronegativity (χ , EN) and electrophilicity index (ω) across the sixteen adenine-initiated DNA trinucleotides.

COSMO surface descriptors and molecular weight

COSMO-derived solvent-accessible surface areas range from 621.0 $\text{\AA}^2$ (ACA) to 786.0 $\text{\AA}^2$ (AGT), and cavity volumes from 936.2 $\text{\AA}^3$ (ACC) to 1002.8 $\text{\AA}^3$ (AGA); together with molecular weight (909.6–989.6 g mol^{-1}), these quantities scale primarily with the steric bulk of the second/third bases (purines contributing larger area/volume increments than

pyrimidines) rather than with electronic structure, reinforcing the separation between steric/solvation properties and frontier-orbital reactivity noted in Correlation analysis.

Biological and methodological implications

The sequence sensitivity of both ΔH_f and the frontier-orbital reactivity indices reported here is consistent with, and complementary to, the established view that local DNA sequence context governs susceptibility to oxidative damage and whole migration efficiency.^[1,2,3,15] While the present AM1/COSMO treatment of isolated, single-stranded trinucleotides cannot capture the full electronic delocalization present in a stacked double helix, it provides a computationally inexpensive, internally consistent first-pass ranking of relative electronic reactivity across sequence space that can guide the selection of candidate motifs for higher-level DFT or ab initio follow-up calculations, and offers a convenient reference data set for structure–reactivity and quantitative structure–property relationship (QSPR) studies of short DNA fragments.

As with any semi-empirical method, AM1-derived absolute orbital energies and heats of formation carry systematic parametrization errors relative to higher-level ab initio or density-functional benchmarks, and Koopmans'-theorem estimates of IP/EA neglect orbital relaxation and electron correlation effects that can shift absolute values by several tenths of an electron volt. The trends and relative rankings reported here — which are the primary quantities of chemical interest in a sequence-scanning study of this kind — are expected to be considerably more robust than the absolute descriptor values themselves.

CONCLUSION

A systematic AM1/COSMO semi-empirical survey of the sixteen adenine-initiated DNA trinucleotides was carried out using MOPAC2016, yielding a self-consistent set of thermodynamic (ΔH_f , dipole moment, COSMO surface area/volume) and quantum-chemical reactivity descriptors (HOMO, LUMO, $E_{\text{HOMO}}-E_{\text{LUMO}}$ gap, ionization potential, electron affinity, electronegativity, chemical hardness, softness, chemical potential, and electrophilicity index) for every sequence. ATT emerged as the thermodynamically most stable trinucleotide and AGG the least stable, while ACT was identified as the most electrophilic sequence and ACG as the most readily oxidized (smallest $E_{\text{HOMO}}-E_{\text{LUMO}}$ gap and highest-lying HOMO). Correlation analysis confirmed the expected algebraic relationships among gap, hardness and softness, while revealing that thermodynamic stability is largely decoupled from electronic reactivity across this sequence set. These results

constitute a compact quantum-chemical reference data set for adenine-led DNA trinucleotide fragments and a methodological template for extending sequence-resolved reactivity mapping to the full 64-member trinucleotide library and to double-stranded contexts in future work.

Disclosure statement

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Author's contribution

The author has participated in conception, design, analysis, interpretation of the data, drafting the article, and approval of the final version.

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