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THERMODYNAMIC STABILITY AND FRONTIER MOLECULAR ORBITAL–DERIVED REACTIVITY DESCRIPTORS OF THYMINE-INITIATED DNA TRINUCLEOTIDES: A SEMI-EMPIRICAL AM1 (MOPAC2016) STUDY

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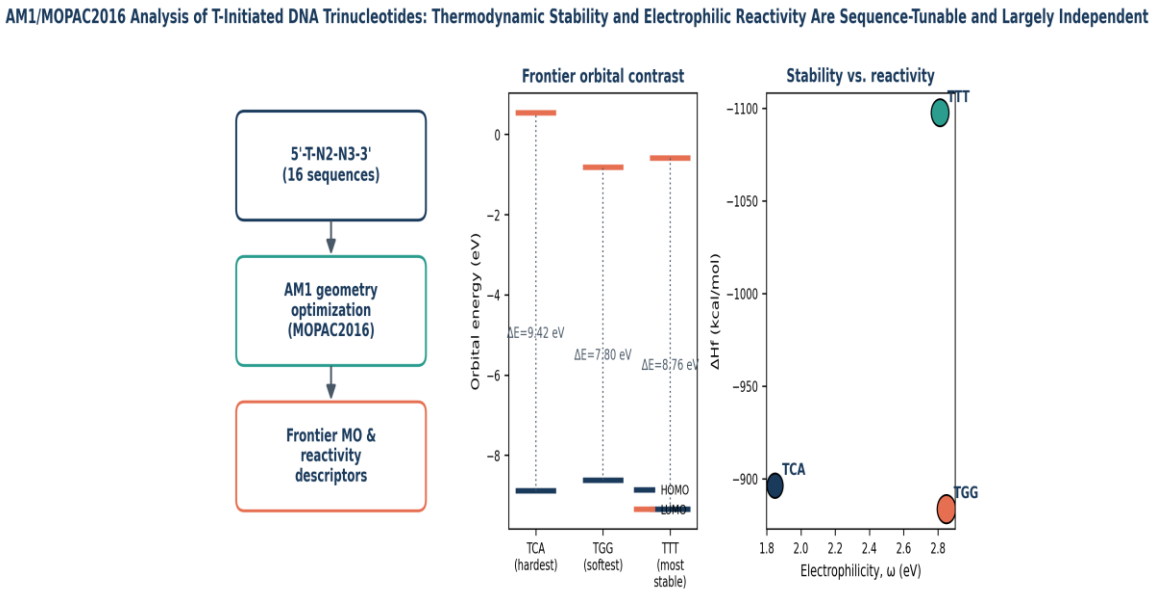
ABSTRACT

DNA trinucleotide fragments contribute to local sequence-dependent stability, charge-transfer behaviour, and susceptibility to oxidative damage, yet the electronic-structure basis of these differences at the trinucleotide level remains incompletely characterized. In this study, all sixteen 5′-Thymine-initiated DNA trinucleotides (5′-T–R–R-3′; R = A, C, G, T) were geometry-optimized using the Austin Model 1 (AM1) semi-empirical Hamiltonian implemented in MOPAC2016 (v23.2.5W). Heats of formation (ΔH_f), dipole moments, frontier molecular orbital (E_{HOMO}/E_{LUMO}) energies, COSMO solvent-accessible surface areas and volumes, and conceptual density-functional-theory global reactivity descriptors—including ionization potential, electron affinity, electronegativity, chemical hardness, softness, chemical potential, and electrophilicity index (ω)—were calculated and systematically compared among the sequences. TTT exhibited the most negative heat of formation (ΔHf = −1097.55 kcal mol^{-1}), whereas TAA showed the least negative value (−801.38 kcal mol^{-1}). Overall, sequences containing predominantly pyrimidine bases displayed more negative heats of formation than sequences enriched in purine bases. The HOMO–LUMO energy gap (ΔE) ranged from 7.80 eV for TGG to 9.42 eV for TCA. As expected from their definitions, ΔE showed an almost perfect positive correlation with

chemical hardness ($r \approx 1.00$) and strong negative correlations with softness ($r = -0.996$) and electrophilicity ($r = -0.953$ for the LUMO-based relationship). The TGG and TGA trinucleotides, characterized by a 5′-GG motif, exhibited relatively small HOMO–LUMO gaps, high dipole moments, and high electrophilicity indices, indicating enhanced electronic softness and susceptibility to electron-transfer processes. These findings are consistent with the established role of guanine-rich DNA sequences as important sites for oxidative charge transfer and damage. The sequence-resolved thermodynamic, structural, and electronic descriptors obtained here provide a compact reference dataset for understanding sequence-dependent DNA reactivity and for developing structure–property relationships relevant to oxidative DNA damage, nucleic-acid-based drug design, and biosensor applications.

KEYWORDS: AM1 semi-empirical method, MOPAC2016, DNA trinucleotides, HOMO–LUMO gap, heat of formation, conceptual density functional theory, electrophilicity index, COSMO.

GRAPHICAL ABSTRACT



Highlights

- All sixteen 5′-thymine-initiated DNA trinucleotides were optimized at the AM1/MOPAC2016 level.
- ΔH_f spans ~300 kcal mol^{-1}; pyrimidine-rich sequences are the most thermodynamically stable (TTT).

- HOMO–LUMO gap ranges from 7.80 eV (TGG) to 9.42 eV (TCA) across the trinucleotide series.
- Guanine-run sequences (TGG, TGA) show the highest electrophilicity, consistent with known DNA oxidation hotspots.
- Thermodynamic stability and electrophilic reactivity vary largely independently, enabling sequence-based tuning.

INTRODUCTION

The sequence-dependent electronic structure of DNA plays an important role in biologically consequential processes, including charge migration through the stacked bases, susceptibility of individual nucleobases to one-electron oxidation, and the thermodynamic stability that contributes to duplex formation, replication fidelity, and mutation processes. Because many sequence-dependent electronic and thermodynamic properties can be characterized at the level of short nucleotide fragments, computational quantum-chemical studies of di- and trinucleotides provide a tractable approach for investigating local sequence-specific reactivity without the computational expense associated with modelling complete DNA duplexes. Among the canonical DNA bases, guanine is particularly susceptible to one-electron oxidation because of its relatively low ionization potential compared with adenine, cytosine, and thymine.[1,2] The electronic properties of guanine are therefore strongly influenced by neighbouring bases and by the local sequence environment. Such sequence-context effects cannot be adequately represented by considering an isolated nucleobase alone, highlighting the importance of systematic investigations at the di- and trinucleotide levels.

In this context, frontier molecular orbital energies, HOMO–LUMO gaps, molecular dipole moments, heats of formation, and conceptual density-functional-theory reactivity descriptors provide useful theoretical measures for comparing the electronic structure and relative reactivity of different DNA sequences. Systematic characterization of these parameters across trinucleotide sequences can help establish sequence–property relationships and identify motifs with distinctive thermodynamic stability or electronic susceptibility relevant to charge-transfer and oxidative-damage processes.

Semi-empirical molecular-orbital methods provide a practical compromise between the computational cost of higher-level ab initio and density-functional-theory (DFT) methods and the need to examine large numbers of related oligonucleotide sequences. The Austin Model 1 (AM1), developed by Dewar and co-workers as an extension and re-parameterization of the

MNDO (Modified Neglect of Diatomic Overlap) framework with additional Gaussian functions in the core–core repulsion term, was designed to improve the treatment of molecular geometries, heats of formation, and hydrogen-bonding interactions relative to earlier semi-empirical approaches.[3,4] Its relatively low computational cost makes AM1 particularly useful for screening systematic series of related molecular structures and for identifying trends in thermochemical properties, dipole moments, and frontier molecular orbital energies. Although semi-empirical methods do not generally provide the same absolute accuracy as higher-level ab initio or DFT calculations, they can nevertheless be valuable for comparative studies in which consistent treatment of a structurally related molecular series is more important than highly accurate absolute energies.[5]

Beyond the direct analysis of frontier molecular orbitals, the conceptual density functional theory (CDFT) framework provides a set of global reactivity descriptors that relate electronic-structure quantities to chemically interpretable measures of molecular reactivity. Chemical hardness (η) describes the resistance of a molecular system to changes in electron number, whereas its reciprocal, softness (S), provides a measure of the ease with which such changes can occur.[6,7] Electronegativity (χ) represents the tendency of a species to attract electron density, while the chemical potential is conventionally defined as $\mu = -\chi$.[7] The electrophilicity index, introduced by Parr, von Szentpály, and Liu, is defined as $\omega = \mu^2/2\eta$ and provides a quantitative measure of the tendency of a molecular system to accept electron density.[8] These descriptors have been widely employed to interpret relative reactivity across organic, pharmaceutical, and biologically relevant molecular systems.

Despite the extensive application of semi-empirical quantum-chemical methods and conceptual-DFT descriptors to nucleic-acid chemistry, a systematic comparison of these parameters across a complete set of sixteen Thymine-initiated DNA trinucleotides remains comparatively limited. The present study, in continuation of research work[13,14] therefore calculates and compares heats of formation (ΔH_f), dipole moments, E_{HOMO} and E_{LUMO} energies, HOMO–LUMO gaps, COSMO surface and volume descriptors, and conceptual-DFT global reactivity indices for the sixteen 5′-T–R–R-3′ trinucleotides using AM1 as implemented in MOPAC2016. The objectives are to (i) establish a consistent reference dataset of thermodynamic, structural, and electronic properties; (ii) identify sequence motifs associated with enhanced thermodynamic stability and distinct electronic reactivity; and (iii) examine whether the calculated sequence-dependent trends are chemically consistent with the

established susceptibility of guanine-containing DNA motifs to oxidative electron-transfer processes.

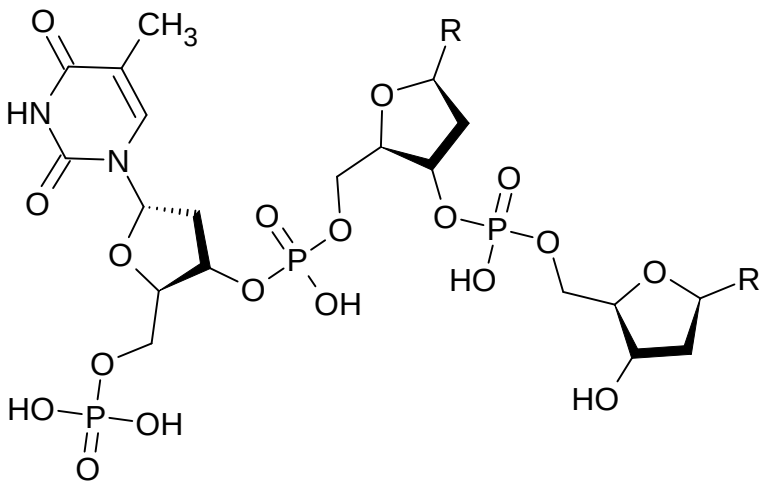


Figure-1:- Thymine-initiated DNA trinucleotides (A,G-purins; C, T - pyrimidines) to generate the sixteeen 5'-T-R-R-3' trinucleotides

Materials and Computational Methodology

Molecular Model and Sequence Selection

All sixteen DNA trinucleotides of the general sequence 5′-T–R–R-3′ (R = A, C, G, T) were considered, representing the complete combinatorial set obtained by fixing thymine at the 5′-terminal position and independently varying the second and third nucleobases (Figure- 1). The resulting sequences were TAA, TAC, TAG, TAT, TCA, TCC, TCG, TCT, TGA, TGC, TGG, TGT, TTA, TTC, TTG, and TTT. Each molecule was constructed as a single-stranded, phosphodiester-linked 2′-deoxyribonucleotide trinucleotide fragment with standard nucleobase connectivity and canonical deoxyribose–phosphate backbone linkages. The molecular models contained a 5′-phosphate terminus and a 3′-hydroxyl terminus. The same terminal-group convention and protonation state were applied consistently to all sixteen sequences so that differences in the calculated thermodynamic and electronic properties could be attributed primarily to sequence composition and position rather than to differences in molecular charge or terminal treatment.

AM1 semi-empirical calculations

Geometry Optimization and Solvation Treatment

Full geometry optimization without symmetry constraints was performed for each trinucleotide at the AM1 level of theory[3,4] using MOPAC2016 (version 23.2.5W) build;

Stewart Computational Chemistry).[9] Geometry optimization was carried out using the eigenvector-following (EF) algorithm. All calculations were performed within the restricted Hartree–Fock (RHF) formalism for closed-shell singlet systems. The same convergence criteria and computational settings were applied consistently to all sixteen trinucleotides to ensure direct comparison of their calculated properties. Solvent effects were incorporated using the conductor-like screening model (COSMO) implemented in MOPAC. COSMO solvent-accessible surface areas and molecular volumes were obtained from the optimized structures using the COSMO formalism developed by Klamt and Schüürmann.[10,11] The same solvation treatment was applied to every trinucleotide so that sequence-dependent differences in the calculated structural and electronic properties could be assessed under consistent environmental conditions.

Derived thermodynamic and electronic properties

For each optimized structure, MOPAC output directly provided the heat of formation (ΔH_f), the ground-state dipole moment, and the energies of the highest occupied and lowest unoccupied molecular orbitals (HOMO, LUMO).

Conceptual density functional theory (global reactivity) descriptors

Using Koopmans'-theorem approximations to the vertical ionization potential ($IP \approx -E_{HOMO}$) and vertical electron affinity ($EA \approx -E_{LUMO}$), the following global reactivity descriptors were computed for every sequence, following the conceptual-DFT formalism of Parr, Pearson, and co-workers[6,7,8]:

- HOMO–LUMO gap: $\Delta E = E_{LUMO} - E_{HOMO}$
- Electronegativity: $\chi = (IP + EA) / 2$
- Global hardness: $\eta = (IP - EA) / 2$
- Global softness: $S = 1 / (2\eta)$
- Chemical potential: $\mu = -\chi$
- Electrophilicity index: $\omega = \mu^2 / (2\eta)$

These six derived descriptors were tabulated alongside the raw HOMO/LUMO energies for all sixteen sequences (Table 2) and used to construct the structure–property correlations discussed. All statistical analyses (descriptive statistics, Pearson correlation coefficients) were performed in Python 3 using pandas and NumPy; figures were generated with Matplotlib.

RESULTS AND DISCUSSION

Computational workflow overview

The overall computational workflow, from sequence input through AM1 geometry optimization to derivation of the conceptual-DFT reactivity descriptors, is summarized schematically in Figure - 2.

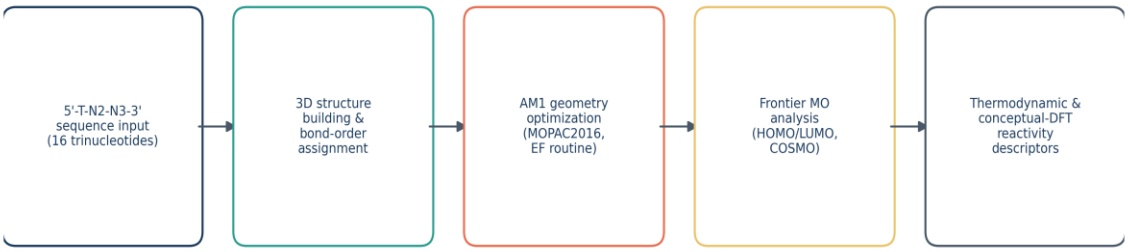


Figure 2: Schematic computational workflow used to obtain thermodynamic and frontier-orbital-derived reactivity descriptors for the sixteen thymine-initiated DNA trinucleotides.

Thermodynamic stability (heat of formation)

The calculated heats of formation (ΔH_f) for the sixteen thymine-initiated DNA trinucleotides are presented in Table - 1 and Figure - 3. The values ranged from −801.38 kcal mol^{-1} for TAA to −1097.55 kcal mol^{-1} for TTT, corresponding to a total range of approximately 296 kcal mol^{-1} across the sequence set. The mean ΔH_f was −942.53 ± 79.37 kcal mol^{-1} (1 standard deviation), demonstrating substantial sequence dependence in the calculated thermochemical properties. A pronounced positional effect was observed for the second nucleotide. Trinucleotides containing a pyrimidine (C or T) at the second position exhibited substantially more negative mean heats of formation than those containing a purine (A or G). The mean ΔHf values were −992.2 kcal mol^{-1} for pyrimidine-N_2 sequences and −892.8 kcal mol^{-1} for purine-N_2 sequences, corresponding to a difference of approximately 99 kcal mol^{-1}. Thus, within the present AM1 model, substitution of the second-position purine by a pyrimidine is associated with a substantial increase in calculated thermodynamic stability.

Table 1: AM1/MOPAC2016-computed thermodynamic, dipole, frontier-orbital, and COSMO surface properties of the sixteen thymine-initiated DNA trinucleotides.

Thymine-initiated DNA Tri-Nucleotides	ΔHf (Kcal/mol)	Dipole Debye	HOMO eV	LUMO eV	Cosmo Area (sq ang) (A^2)	Cosmo volume (cu ang) (A^3)	Mol wt
TAA	-801.3810	8.927	-8.945	-0.443	734.04	957.96	948.6290
TCA	-896.1872	8.002	-8.885	0.537	650.21	948.41	924.6040
TGA	-845.0289	6.663	-8.690	-0.407	767.66	989.22	964.6284
TTA	-964.9908	2.768	-8.824	-0.363	707.91	960.78	939.6156
TAC	-895.2003	8.157	-8.589	-0.485	704.03	959.00	924.6040
TCC	-978.9921	5.441	-9.397	-0.323	703.54	910.41	900.5790
TGC	-925.2656	11.159	-8.839	-0.542	739.71	950.73	940.6034
TTC	-1041.8634	3.478	-9.407	-0.333	693.40	956.49	915.5906
TAG	-855.6844	4.512	-8.558	-0.466	784.58	975.49	964.6284
TCG	-927.1459	10.969	-8.892	-0.595	734.34	969.44	940.6034
TGG	-883.5311	15.079	-8.618	-0.814	710.66	1002.04	980.6278
TTG	-992.3004	4.978	-8.709	-0.704	708.26	969.35	955.6150
TAT	-955.6282	6.710	-8.929	-0.475	745.11	957.78	939.6156
TCT	-1038.7464	3.721	-9.380	-0.503	761.16	941.58	915.5906
TGT	-980.9377	10.668	-8.814	-0.537	781.27	989.68	955.6150
TTT	-1097.5469	12.021	-9.344	-0.584	756.18	970.10	930.6022

This pronounced sequence dependence indicates that the identity of the central base can strongly influence the optimized electronic and structural characteristics of the trinucleotide. However, the ΔH_f data alone do not establish a specific molecular origin for this effect. Differences in backbone conformation, intramolecular hydrogen bonding, electrostatic interactions, base orientation, and overall molecular geometry may all contribute to the calculated heat of formation. Therefore, the observed pyrimidine-associated stabilization should be regarded as a sequence-dependent AM1 result rather than attributed solely to the smaller size of the pyrimidine ring system.

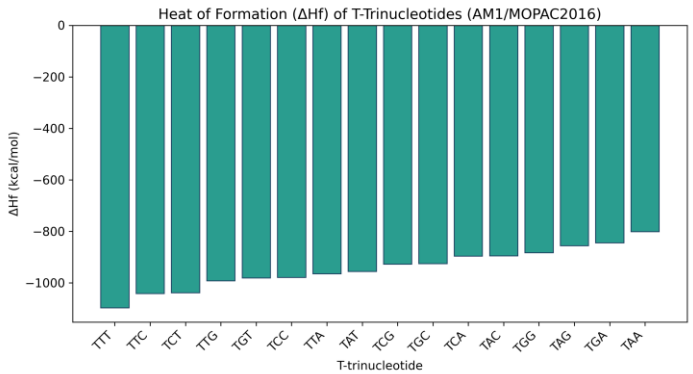


Figure – 3: Computed heat of formation (ΔHf, kcal mol^{-1}) for the sixteen thymine-initiated DNA trinucleotides, ranked from least stable (TAA) to most stable (TTT).

Dipole Moments and Sequence Dependence

The calculated ground-state dipole moments exhibited more than a five-fold variation across the sixteen trinucleotides, ranging from 2.77 D for TTA to 15.08 D for TGG (Table - 1). The largest dipole moments were obtained for TGG (15.08 D) and TCG (10.97 D), both of which contain guanine within the variable positions of the trinucleotide. The relatively large dipole moments of these sequences may reflect the pronounced heterogeneous distribution of electron density associated with the multiple heteroatom-containing functional groups of guanine, together with the sequence-dependent optimized molecular geometry. Despite this substantial variation in molecular polarity, the dipole moment exhibited only a weak correlation with the calculated heat of formation across the complete sequence set (Pearson r = 0.17). This weak relationship indicates that overall molecular polarity does not serve as a strong predictor of the calculated thermodynamic stability within these trinucleotides. Instead, the heat of formation appears to depend on a combination of electronic structure, backbone conformation, intramolecular interactions, and sequence-dependent geometry. Thus, dipole moment and thermodynamic stability provide complementary rather than interchangeable measures of the molecular properties of the thymine-initiated DNA trinucleotides.

Frontier Molecular Orbitals and HOMO–LUMO Gaps

The calculated frontier molecular orbital energies for all sixteen trinucleotides are presented as an orbital energy-level diagram in Figure - 4. The HOMO energies exhibited a relatively narrow range, from −8.59 eV for TAC to −9.41 eV for TTC and TCC, whereas the LUMO energies showed a considerably broader distribution, ranging from −0.81 eV for TGG to +0.54 eV for TCA. This difference indicates that, within the present AM1 calculations, the unoccupied molecular-orbital manifold is more sensitive to sequence variation than the occupied manifold. The resulting HOMO–LUMO energy gaps (ΔE; Figure 4) ranged from 7.80 eV for TGG to 9.42 eV for TCA, with a mean value of 8.49 eV. TGG exhibited the smallest gap in the series, while TGA had the third-smallest gap (8.28 eV). The particularly small gap calculated for TGG is noteworthy because this sequence contains a consecutive 5′-GG motif, which is well established as an electronically favourable site for hole localization and one-electron oxidation in DNA [1,2]. The low calculated LUMO energy and relatively small HOMO–LUMO separation of TGG therefore provide a qualitative indication of enhanced electronic softness within this sequence.

Table 2: Derived conceptual-DFT global reactivity descriptors of the sixteen thymine-initiated DNA trinucleotides (all energies in eV; softness S in eV^{-1}).

Thymine-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)	Eletrophilicity Index (ω)
TAA	-8.945	-0.443	8.502	8.945	0.443	4.694	4.251	1.052	-4.694	2.592
TCA	-8.885	0.537	9.422	8.885	-0.537	4.174	4.711	0.943	-4.174	1.849
TGA	-8.690	-0.407	8.283	8.690	0.407	4.549	4.142	1.049	-4.549	2.498
TTA	-8.824	-0.363	8.461	8.824	0.363	4.594	4.231	1.043	-4.594	2.494
TAC	-8.589	-0.485	8.104	8.589	0.485	4.537	4.052	1.060	-4.537	2.540
TCC	-9.397	-0.323	9.074	9.397	0.323	4.860	4.537	1.036	-4.860	2.603
TGC	-8.839	-0.542	8.297	8.839	0.542	4.691	4.149	1.065	-4.691	2.652
TTC	-9.407	-0.333	9.074	9.407	0.333	4.870	4.537	1.037	-4.870	2.614
TAG	-8.558	-0.466	8.092	8.558	0.466	4.512	4.046	1.058	-4.512	2.516
TCG	-8.892	-0.595	8.297	8.892	0.595	4.744	4.149	1.072	-4.744	2.712
TGG	-8.618	-0.814	7.804	8.618	0.814	4.716	3.902	1.104	-4.716	2.850
TTG	-8.709	-0.704	8.005	8.709	0.704	4.707	4.003	1.088	-4.707	2.767
TAT	-8.929	-0.475	8.454	8.929	0.475	4.702	4.227	1.056	-4.702	2.615
TCT	-9.380	-0.503	8.877	9.380	0.503	4.942	4.439	1.057	-4.942	2.751
TGT	-8.814	-0.537	8.277	8.814	0.537	4.676	4.139	1.065	-4.676	2.641
TTT	-9.344	-0.584	8.760	9.344	0.584	4.964	4.380	1.067	-4.964	2.813

The relatively small gap of TGA, despite the absence of a terminal guanine, suggests that the electronic response of a trinucleotide cannot be attributed solely to the identity of the terminal base. Instead, the positional arrangement of the bases and their influence on the optimized electronic structure contribute to the frontier-orbital properties. Overall, the correspondence between the particularly small AM1-derived gap of the GG-containing TGG sequence and the established susceptibility of consecutive guanine motifs to oxidative charge-transfer processes provides a useful qualitative chemical consistency check on the calculated sequence-dependent trends. However, the HOMO–LUMO gap alone should not be interpreted as a direct quantitative measure of oxidation potential or hole-transfer rate.

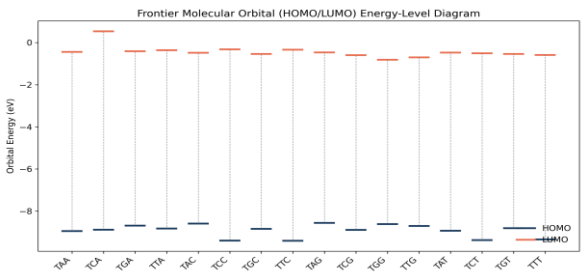


Figure 4: Frontier molecular orbital (HOMO/LUMO) energy-level diagram for the sixteen T-initiated DNA trinucleotides. Dotted vertical lines span the HOMO–LUMO gap for each sequence.

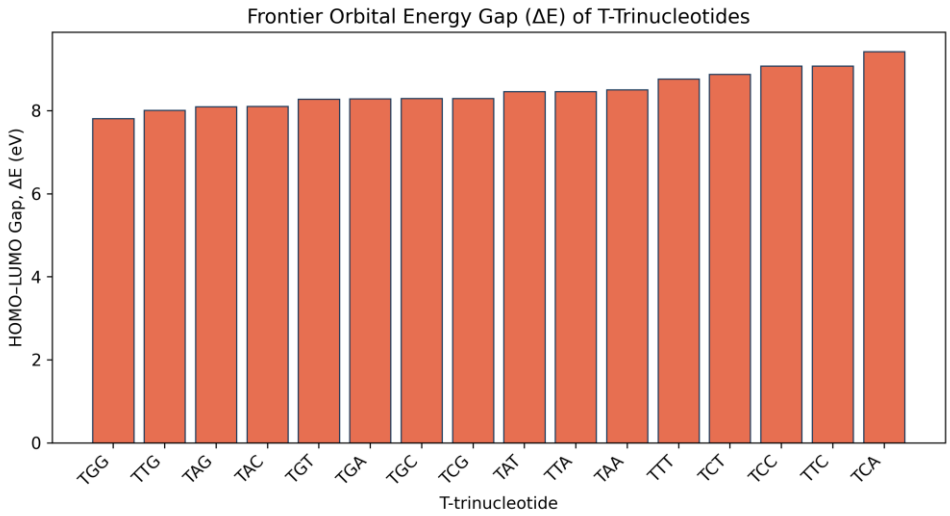


Figure 5: HOMO–LUMO energy gap (ΔE, eV) of the sixteen thymine-initiated DNA trinucleotides, ranked from smallest (TGG, most kinetically reactive) to largest (TCA, most kinetically inert) gap.

Conceptual-DFT Global Reactivity Descriptors

The complete set of conceptual-DFT global reactivity descriptors derived from the calculated frontier orbital energies is presented in Table - 2. As expected from the definitions employed in the present analysis, the global chemical hardness (η) followed the HOMO–LUMO energy gap almost exactly, because $\eta = \Delta E/2$ under the Koopmans-based approximation used here. Consequently, η and ΔE exhibited an essentially perfect positive correlation across the sixteen trinucleotides (Pearson $r \approx 1.00$). Softness (S), defined as the reciprocal of hardness, showed the expected inverse relationship with η and exhibited a strong negative correlation with the calculated LUMO energies ($r = -0.996$) within the present sequence set.

The electrophilicity index (ω), which combines chemical potential and hardness according to $\omega = \mu^2/2\eta$, varied substantially among the trinucleotides. The highest value was obtained for TGG (ω = 2.850 eV), followed by TTT (ω = 2.813 eV), whereas TCA exhibited the lowest electrophilicity index (ω = 1.849 eV). Electrophilicity showed a strong negative correlation with LUMO energy ($r = -0.953$), indicating that, within this particular series, sequences with more favourable LUMO energies tended to exhibit larger calculated electrophilicity indices. This relationship should nevertheless be interpreted as a sequence-specific correlation rather than as a general equivalence between LUMO energy and electrophilicity, because ω is determined jointly by chemical potential and hardness.

A clear positional trend was also observed for the second base. Trinucleotides containing a pyrimidine at the second position exhibited a higher mean chemical hardness than those containing a purine at that position (mean η = 4.373 eV versus 4.114 eV). The corresponding pyrimidine-N_2 sequences therefore tended, on average, toward electronically harder and less soft character. In contrast, TGG, which contains guanine at both variable positions, was the softest sequence in the series (η = 3.902 eV) and also exhibited the highest electrophilicity index (ω = 2.850 eV).

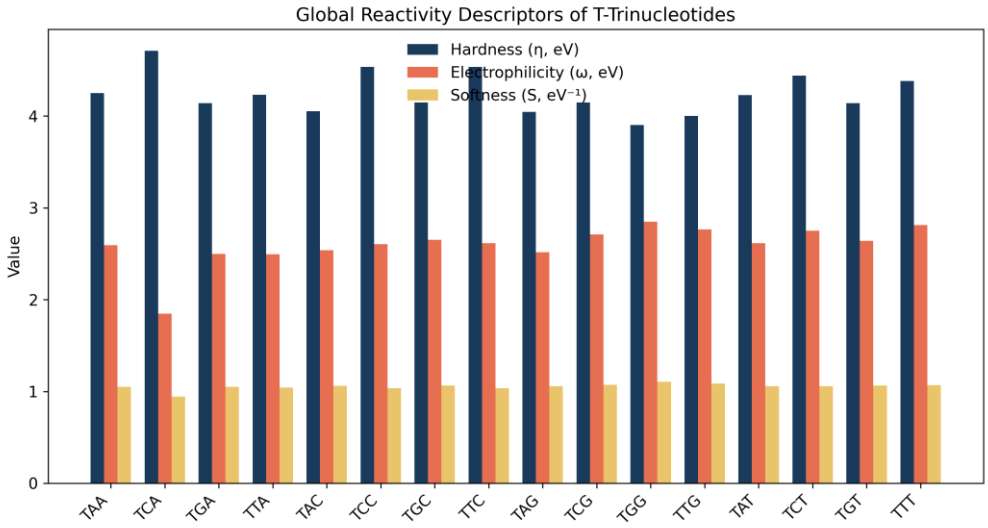


Figure 6: Global reactivity descriptors — hardness (η), electrophilicity index (ω), and softness (S) — for the sixteen thymine-initiated DNA trinucleotides.

The distinctive electronic behaviour of TGG is qualitatively consistent with the established role of consecutive guanine residues in DNA oxidation and charge-transfer chemistry [1,2]. In particular, the presence of adjacent guanines is associated with relatively favourable hole localization and low oxidation thresholds. The agreement between the calculated softness/electrophilicity of TGG and the known oxidative susceptibility of guanine-rich DNA provides supportive qualitative evidence that the AM1-derived descriptors capture chemically meaningful sequence-dependent electronic differences. Nevertheless, these conceptual-DFT descriptors should be regarded as comparative indicators within the present computational model rather than direct substitutes for experimentally measured oxidation potentials or charge-transfer rates.

Cross-Correlation Analysis of Molecular Descriptors

The cross-correlation matrix of the calculated and derived molecular descriptors is presented in Figure - 7 and reveals three principal patterns.

First, the conceptual-DFT descriptors derived from the frontier orbital energies exhibit the expected strong internal correlations. In particular, the HOMO–LUMO gap and chemical hardness are essentially perfectly correlated (ΔE–η, $r \approx 1.00$), while softness shows a strong inverse relationship with the corresponding frontier-orbital quantities (S–LUMO, $r = -0.996$). These relationships primarily reflect the mathematical definitions of the descriptors and therefore provide an internal consistency check on the calculations rather than independent evidence of new chemical relationships.

Second, the calculated heat of formation (ΔH_f) exhibited a moderate positive correlation with molecular weight ($r = 0.52$), whereas its correlation with dipole moment was weak ($r = 0.17$). The moderate association with molecular weight indicates that molecular size contributes to the variation in the calculated thermochemical values, but the relatively broad ΔH_f range cannot be explained by molecular mass alone. Similarly, the weak ΔH_f–dipole correlation suggests that overall molecular polarity is not a dominant determinant of the calculated thermodynamic stability across the sequence set. Sequence-dependent electronic structure and optimized molecular geometry are therefore likely to contribute substantially to the observed variation.

Third, LUMO energy, softness, and electrophilicity formed a relatively distinct correlated group, with substantially weaker relationships to the ΔH_f/molecular-weight variables. This separation indicates that thermodynamic stability and frontier-orbital-derived reactivity are not simply interchangeable properties within the present trinucleotide series. Consequently, sequence variation may provide a means of obtaining different combinations of thermodynamic and electronic characteristics. This observation is potentially useful for the rational design of nucleic-acid fragments in which relative stability and electronic reactivity are both important considerations, although the extent to which these properties can be independently controlled would require validation using additional computational methods and experimental measurements.

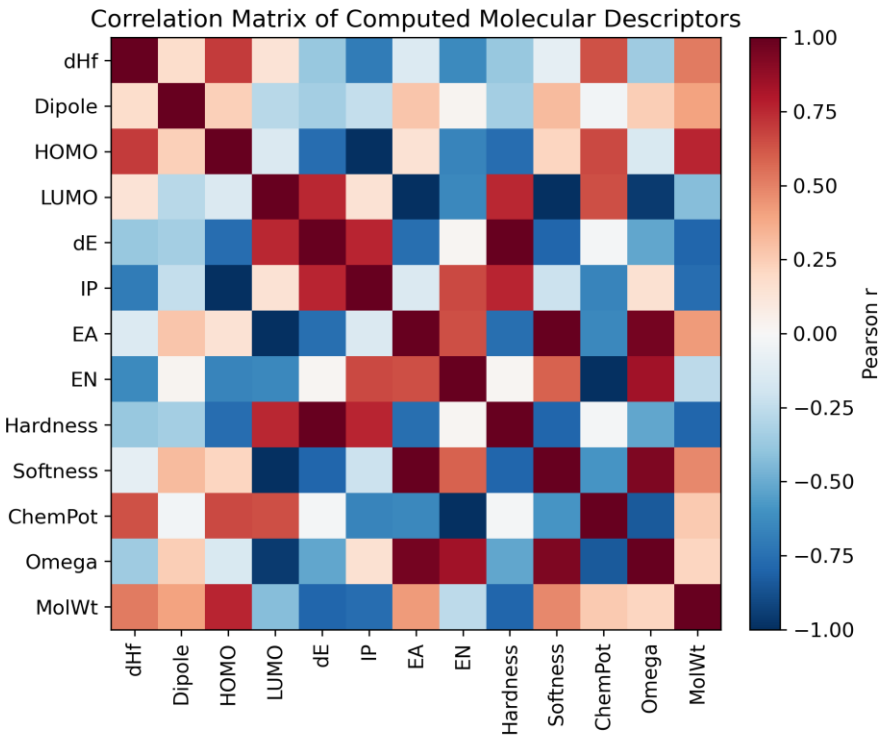


Figure 7: Pearson correlation matrix among the thirteen thermodynamic, frontier-orbital, and conceptual-DFT descriptors computed for the sixteen thymine-initiated DNA trinucleotides.

Dipole Moment–Heat of Formation Relationship

Finally, the dipole moment versus heat of formation (ΔH_f) scatter plot, with the points color-coded according to their HOMO–LUMO gaps (Figure - 8), provides a useful visual representation of the multidimensional sequence dependence of the calculated properties. The plot distinguishes sequences such as TTA and TCA, which combine relatively low dipole moments with comparatively large HOMO–LUMO gaps, from sequences such as TGG and TCG, which exhibit higher dipole moments and smaller gaps. These contrasting profiles demonstrate that sequence variation can simultaneously influence molecular polarity and frontier-orbital characteristics, while the weak correlation between dipole moment and ΔH_f indicates that these properties are not directly coupled across the complete sequence set.

The particularly distinct electronic profile of TGG—high dipole moment together with the smallest HOMO–LUMO gap in the series—is consistent with its enhanced electronic softness and electrophilicity identified from the conceptual-DFT analysis. Thus, Figure – 8 provides a complementary visualization of the sequence-dependent relationship between thermodynamic, electrostatic, and frontier-orbital properties and reinforces the conclusion

that no single descriptor is sufficient to characterize the overall reactivity of these DNA trinucleotides.

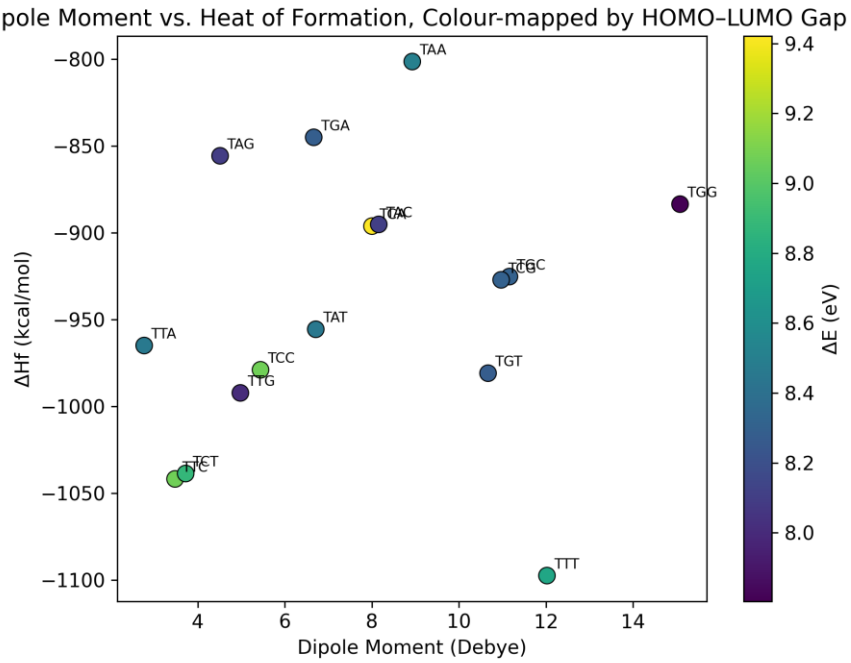


Figure 8: Dipole moment versus heat of formation for the sixteen thymine-initiated DNA trinucleotides, colour-mapped by HOMO–LUMO gap (ΔE).

CONCLUSIONS

AM1/MOPAC2016 calculations on the complete set of sixteen 5′-thymine-initiated DNA trinucleotides demonstrate substantial sequence dependence in both thermodynamic and electronic properties. The calculated heat of formation (ΔH_f) identifies TTT as the most thermodynamically stable sequence, whereas TAA exhibits the least negative ΔH_f. In contrast, frontier-orbital characteristics show a different sequence dependence, with TGG exhibiting the smallest HOMO–LUMO gap, the largest dipole moment, and the highest calculated electrophilicity index. The distinctive electronic properties of TGG are qualitatively consistent with the established susceptibility of guanine-rich DNA, particularly consecutive guanine (5′-GG) motifs, to one-electron oxidation and oxidative damage. The analysis further demonstrates that thermodynamic stability and frontier-orbital-derived reactivity are not strongly correlated across the complete sequence set. Global hardness and softness closely track the HOMO–LUMO gap by definition and therefore function primarily as convenient quantitative measures of frontier-orbital separation rather than as independent structural descriptors. The correlation analysis also indicates that molecular polarity,

thermodynamic stability, and electrophilicity capture complementary aspects of sequence-dependent molecular behaviour.

The combined dataset presented in Tables - 1 and - 2 therefore provides a compact and internally consistent reference for comparing the thermodynamic, structural, electrostatic, and electronic properties of thymine-initiated DNA trinucleotides. These results may contribute to the theoretical interpretation of sequence-dependent oxidative DNA reactivity and provide preliminary structure–property relationships relevant to the design of nucleic-acid-based sensors and other functional molecular systems. They may also serve as a useful starting point for benchmarking higher-level quantum-chemical calculations on larger nucleic-acid fragments. Future investigations should extend the present analysis to double-stranded DNA models incorporating complementary strands, explicit or hybrid hydration environments, and counter-ion effects. Comparison with higher-level DFT and, where computationally feasible, ab initio calculations would further establish the robustness of the AM1-derived sequence trends. Experimental measurements of oxidation potentials and charge-transfer behaviour would provide an additional basis for determining how reliably the calculated descriptors predict biologically relevant DNA reactivity.

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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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