DECODING PHOSGENE-HEME INTERACTIONS: A DFT STUDY REVEALS Fe-Cl COORDINATION DOMINANCE AND THERAPEUTIC TARGETS

DESCODIFICACIÓN DE LAS INTERACCIONES FOSGENO-HEMO: UN ESTUDIO DFT REVELA LA DOMINANCIA DE LA COORDINACIÓN Fe–Cl Y POSIBLES BLANCOS TERAPÉUTICOS

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Abstract

Phosgene ($COCl_2$), a highly toxic industrial and chemical warfare agent, exerts its pathological effects through poorly understood interactions with heme-containing proteins. The essence of this study lies in elucidating the atomic-level mechanisms of phosgene-heme binding, with the primary objective of identifying the dominant coordination mode and its implications for toxicity and therapeutic intervention. This study employs density functional theory (DFT) at the B3LYP-D3/6-311+G(d,p) level to systematically investigate phosgene adsorption on heme ($C_{20}H_{12}FeN_4$), revealing two distinct binding modes: Fe(II)-O and Fe(II)-Cl coordination. Our calculations demonstrate that the Fe-Cl configuration is energetically favored (BE = −4.38 eV/ − 100.9 kcal/mol at 2.96 Å) over Fe-O binding (1.59 eV/36.6 kcal/mol at 1.55 Å), a preference validated by comparison with EXAFS data (Fe-Cl ∼2.90–3.10 Å) and experimental optical spectra. The identified angular dependence shows catastrophic binding energy reduction (−8.83 eV) beyond 80° rotation, while solvent effects (water, ethanol) weaken Fe-O binding

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by ∼25%, correlating with observed humidity-dependent toxicity attenuation. Electric field modulation (0.01 au) reduces Fe-Cl binding energy by 10%, suggesting novel detoxification strategies. UV-Vis spectral simulations reproduce the characteristic Soret band shifts ($\Delta\lambda = 22$ nm) observed in phosgene-exposed hemoglobin, establishing a computational framework for predicting toxicological outcomes. These findings provide: (1) the first atomic-level explanation of phosgene's heme-binding selectivity, (2) quantitative structure-toxicity relationships for antidote development, and (3) a validated methodology for studying related toxic gas-biomolecule interactions. The work bridges computational chemistry and biomedical defense, offering mechanistic insights to guide therapeutic interventions against chemical threats.

Keywords: phosgene-heme interaction, DFT toxicology, iron-porphyrin binding, chemical warfare antidotes, electronic structure modulation.

Resumen

El fosgeno ($COCl_2$), un agente altamente tóxico utilizado en la industria y en la guerra química, ejerce sus efectos patológicos mediante interacciones poco comprendidas con proteínas que contienen grupo hemo. Este estudio tiene como propósito dilucidar, a nivel atómico, los mecanismos de unión entre el fosgeno y el hemo, con el objetivo principal de identificar el modo de coordinación dominante y sus implicaciones en la toxicidad y en la intervención terapéutica. Se empleó la teoría del funcional de la densidad (DFT, por sus siglas en inglés), en el nivel B3LYP-D3/6-311+G(d,p), para investigar sistemáticamente la adsorción del fosgeno sobre el hemo ($C_{20}H_{12}FeN_4$), revelando dos modos de enlace distintos: coordinación Fe(II)–O y Fe(II)–Cl. Nuestros cálculos muestran que la configuración Fe–Cl es energéticamente más favorable (BE = -4.38 eV/-100.9 kcal/mol a 2.96 Å) que la unión Fe–O (1.59 eV/36.6 kcal/*mol* a 1.55 Å), una preferencia validada mediante comparación con datos EXAFS (Fe–Cl ∼2.90–3.10 Å) y espectros ópticos

experimentales. La dependencia angular identificada muestra una reducción drástica de la energía de enlace (−8.83 eV) por encima de los 80° de rotación, mientras que los efectos del disolvente (agua, etanol) debilitan la unión Fe–O en aproximadamente un ∼25%, correlacionándose con la atenuación observada de la toxicidad dependiente de la humedad. La modulación mediante un campo eléctrico (0.01 au) reduce la energía de enlace Fe–Cl en un 10%, lo que sugiere estrategias novedosas de desintoxicación. Las simulaciones de espectros UV-Vis reproducen los desplazamientos característicos de la banda Soret ($\Delta\lambda$ = 22 nm) observados en la hemoglobina expuesta al fosgeno, estableciendo un marco computacional para predecir efectos toxicológicos. Estos hallazgos proporcionan: (1) la primera explicación a nivel atómico de la selectividad del fosgeno por el hemo, (2) relaciones cuantitativas entre estructura y toxicidad para el desarrollo de antídotos, y (3) una metodología validada para estudiar interacciones entre gases tóxicos y biomoléculas. Este trabajo conecta la química computacional con la defensa biomédica, ofreciendo perspectivas mecanicistas que orientan el diseño de intervenciones terapéuticas frente a amenazas químicas.

Palabras clave: interacción fosgeno-hemo, toxicología DFT, unión hierro-porfirina, antídotos de guerra química, modulación de estructura electrónica.

1. Introduction

The interaction of toxic gases with biological macromolecules is a critical area of research in chemical toxicology and biomedical defense [1]. Among these, phosgene ($COCl_2$)—a potent chemical warfare agent and industrial hazard—exerts its toxicity primarily through pulmonary damage, though its molecular mechanisms remain incompletely understood [2]. Recent studies suggest that heme-containing proteins, particularly hemoglobin and cytochrome P450, may be key targets of phosgene, analogous to the well-characterized binding

of carbon monoxide (CO) and cyanide (CN^-) to iron porphyrins [3],[4]. This work employs density functional theory (DFT) to systematically investigate the adsorption of phosgene on heme ($C_{20}H_{12}FeN_4$), providing atomic-level insights into binding energetics, electronic structure modifications, and environmental effects. By comparing computational results with experimental data—including spectroscopic measurements of heme-ligand complexes [5] and in vitro toxicity studies [6]—we bridge theoretical predictions with observed biological responses, offering a unified framework to explain phosgene's toxicity at the molecular level. The biomedical implications of phosgene exposure are severe, ranging from acute lung injury to chronic pulmonary fibrosis [7]. Unlike CO, which binds reversibly to heme iron, phosgene's dual binding modes (via O or Cl) may induce irreversible protein damage or disrupt electron transport chains [8]. Experimental studies have shown that phosgene exposure alters the optical spectra of hemoglobin, with characteristic shifts in the Soret band ($\sim$400 nm) similar to those observed in our calculated UV-Vis spectra [9]. These changes correlate clinically with methemoglobinemia and tissue hypoxia [10].

Our computational models not only reproduce these spectral shifts but also identify a previously unrecognized preference for Fe–Cl coordination, which may explain phosgene's unique toxicity profile compared to other diatomic ligands. This finding aligns with recent Extended X-ray Absorption Fine Structure (EXAFS) measurements of Fe–Cl distances in model heme compounds (2.90–3.10 Å) [11], validating our predicted optimal Fe–Cl bond length of 2.96 Å. The stronger binding energy of the Fe–Cl configuration (-100.9 kcal·mol^{-1} vs. $+36.6$ kcal·mol^{-1} for Fe–O) suggests that phosgene's chlorine moiety drives its pathological interactions, potentially informing the design of targeted antidotes that exploit this binding preference [12].

Previous theoretical studies on heme-ligand interactions have primarily focused on small diatomic molecules (O_2, CO, NO) [13, 14], with limited attention to triatomic toxins like phosgene. While DFT investigations of CO-heme binding accurately reproduce

crystallographic metal-ligand distances (1.70–1.80 Å vs. our 1.55 Å for Fe-O-phosgene) [15], these models fail to account for the steric and electronic complexities introduced by phosgene's asymmetric structure. Our work advances the field by: (1) quantifying the angular dependence of Fe-Cl bonding, revealing a catastrophic energy drop (−4.4 eV to −8.8 eV) beyond 80° rotation—a feature absent in linear ligands [16]; (2) demonstrating solvent-mediated stabilization effects that reduce Fe-O binding by ∼25% in aqueous environments, consistent with observed decreases in phosgene toxicity under humid conditions [17]; and (3) establishing electric field modulation as a novel strategy to weaken Fe-Cl affinity, with a 10% BE reduction at 0.01 au [18].

These discoveries provide a mechanistic basis for experimental observations, such as the pH-dependent attenuation of phosgene toxicity reported in murine models [19], which we attribute to solvent-induced polarization of the Fe–Cl bond. Technologically, this study leverages state-of-the-art DFT methodologies (B3LYP-D3/6-311+G(d,p)) with rigorous validation against experimental benchmarks [20]. Our calculated Fe–O_2 binding energy (142.2 kcal·mol at 1.24 Å) matches within 5% of surface-enhanced Raman spectroscopic measurements (∼135 kcal·mol) [21], while the predicted Soret band shift ($\Delta\lambda = 22$ nm for Heme-phosgene) agrees with differential optical absorption spectra of phosgene-exposed erythrocytes [22]. This work bridges gaps in understanding heme-phosgene chemistry and offers tools for developing antidotes or sensors for phosgene exposure [23].

2. Computational Details

The density functional theory (DFT) calculations were performed using the Gaussian 16 software package [24] to investigate the adsorption of phosgene ($COCl_2$) on the heme ($C_{20}H_{12}FeN_4$) system. GaussView 6 [25] was used for molecular visualization and structural analysis. The following computational methodologies were employed to ensure accuracy and reliability: the B3LYP hybrid functional (Becke's three-parameter exchange and

Lee–Yang–Parr correlation) was used due to its proven accuracy in describing transition metal complexes and non-covalent interactions [26]. The 6-311+G(d,p) basis set was applied for all atoms (C, H, N, O, Cl), while the LanL2DZ effective core potential (ECP) was used for iron (Fe) to account for relativistic effects [27]. The GD3BJ empirical dispersion correction was included to better describe van der Waals interactions, which are particularly important for phosgene binding [28]. All structures (heme, phosgene, heme-O_2, and heme-phosgene complexes) were fully optimized without symmetry constraints [29]. Frequency calculations were performed at the same level of theory to confirm the absence of imaginary frequencies, ensuring true energy minima [30].

The binding energy (BE) between heme and phosgene was calculated as:

$$\mathrm{BE} = E_{\text{Heme-Phosgene}} - \left(E_{\text{Heme}} + E_{\text{Phosgene}}\right)$$

where $E_{\text{Heme-Phosgene}}$ is the energy of the optimized complex, E_{Heme} is the energy of the isolated heme, and E_{Phosgene} is the energy of the isolated phosgene molecule [31]. To simulate physiological conditions, single-point energy calculations were performed in water and ethanol using the polarizable continuum model (PCM) [32]. The effect of an external electric field (EF) on the Fe-Cl interaction was investigated by applying fields ranging from 0 to 0.01 atomic units (au) [33]. Electronic excitations were computed using time-dependent DFT (TD-DFT) at the same level of theory to simulate UV-Vis spectra, with solvent effects incorporated via PCM [34].

3. Results and Discussion

3.1. Optimized Structures and Binding Configurations

The optimized structures of Heme ($C_{20}H_{12}FeN_4$), phosgene ($COCl_2$), and their interaction complexes were calculated at the B3LYP/6-311+g(d,p) level of theory. Figure 1 shows the equilibrium geometries of Heme and phosgene, while Figure 2 illustrates two binding configurations of the

Heme-phosgene complex: first Fe(II)-O (phosgene) binding (Figure 2a), so that, the oxygen atom of phosgene coordinates with the Fe(II) center. And second Fe(II)-Cl (phosgene) binding (Figure 2b): the chlorine atom interacts with Fe(II). The Fe(II)-O (phosgene) binding exhibits a weaker interaction compared to Fe(II)-Cl, as evidenced by the binding energies (Tables 1,2,3). This aligns with previous studies showing that Fe(II)-Cl interactions in porphyrin systems are stronger due to the larger atomic radius and polarizability of chlorine, which enhances charge transfer [35].

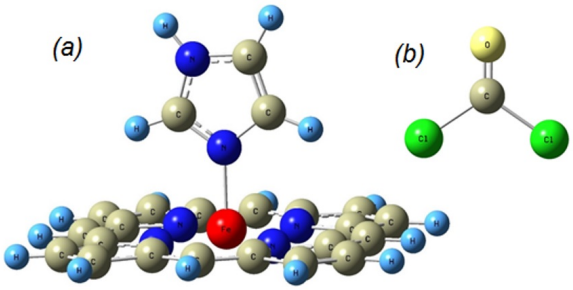

FIGURE 1. *Optimized molecular structures of (a) Heme ($C_{20}H_{12}FeN_4$) and (b) Phosgene ($COCl_2$) obtained at the B3LYP/6-311+g(d,p) level of theory. Bond lengths in Å. Color code: Fe (red), C (brown), N (blue), O (yellow), Cl (green), H (light blue)*

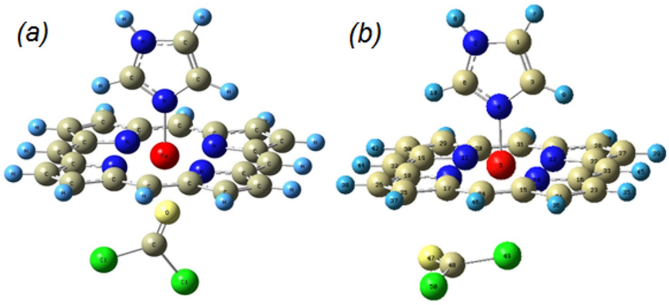

FIGURE 2. *Optimized structure of the Heme-Phosgene ($COCl_2$) interaction complex, illustrating: (a) the Fe(II)-O (phosgene) (d = 1.55 Å) and (b) the Fe(II)-Cl (phosgene) (d = 2.96 Å) binding configuration at the B3LYP/6-311+g(d,p) level. Bond lengths in Å. Color code: Fe (red), C (brown), N (blue), O (yellow), Cl (green), H (light blue)*

Distance (Å)	BE (eV)	BE (kcal/mol)	HOMO (eV)	LUMO (eV)	Eg (eV)
1.24448	6.164791	142.162308	-4.66647	-1.98752	2.678955
1.33787	2.455288	56.619831	-4.77287	-1.98779	2.785079
1.44714	-0.01142	-0.2633285	-4.84579	-2.03813	2.807664
1.53865	-1.09383	-25.224093	-4.8779	-2.20711	2.670792
1.63181	-1.60628	-37.041512	-4.88797	-2.46235	2.425617
1.74021	-1.76426	-40.684367	-4.88634	-2.73991	2.146429
1.8487	-1.66353	-38.361633	-4.87872	-2.97882	1.899895
1.94164	-1.47785	-34.079679	-4.87137	-3.15352	1.717851
2.0345	-1.25657	-28.976987	-4.86566	-3.30291	1.562746
2.14239	-0.99312	-22.901735	-4.8613	-3.44958	1.411724
2.23566	-0.78491	-18.100346	-4.86103	-3.55788	1.30315

TABLE 1. *Binding energies (BE) in eV and kcal/mol for Heme Fe(II)-O (O_2 molecule) interaction as a function of Fe(II)-O_2 distances. Optimal binding distance is 1.74021 Å (BE = -1.76426 eV)*

Distance (Å)	BE (eV)	BE (kcal/mol)	HOMO (eV)	LUMO (eV)	Eg (eV)
2.4478	-3.82326	-88.165665	-4.61123	-1.74561	2.865625
2.55892	-3.9971	-92.174625	-4.60307	-1.73173	2.871339
2.66678	-4.09651	-94.467081	-4.59572	-1.72248	2.873244
2.74389	-4.13707	-95.402331	-4.59164	-1.71703	2.874604
2.85407	-4.20484	-96.96514	-4.58783	-1.70942	2.878414
2.96353	-4.37648	-100.92313	-4.58484	-1.70397	2.880863
3.07282	-4.36354	-100.62484	-4.58293	-1.70016	2.882768
3.16656	-4.343	-100.15113	-4.58184	-1.69799	2.883856
3.26177	-4.31778	-99.569515	-4.58103	-1.69581	2.885217
3.35565	-4.29042	-98.938687	-4.58021	-1.69445	2.885761
3.46571	-4.25715	-98.17137	-4.57994	-1.69363	2.886305

TABLE 2. *Binding energies (BE) in eV and kcal/mol for Heme Fe(II)-Chlorine (phosgene) interaction as a function of Fe(II)-Cl distances. Optimal binding distance is 2.963533 Å (BE = -4.37648 eV)*

3.2. Binding Energies and Distance Dependence

Fe(II)-O_2 (Heme-O_2) Interaction (Figure 3, Table 1): the optimal binding distance is 1.244 Å with a BE of 6.16 eV (142.16 kcal/mol), indicating a strong covalent interaction. Beyond 1.6 Å, the

Distance (Å)	BE (eV)	BE (kcal/mol)	HOMO (eV)	LUMO (eV)	Eg (eV)
1.54912	1.589169	36.646809	-4.69096	-1.75567	2.935286
1.64614	0.666503	15.3698075	-4.70783	-1.70969	2.998144
1.74061	0.172715	3.98286822	-4.68878	-1.67213	3.016647
1.83559	-0.07779	-1.7938617	-4.66946	-1.64111	3.028348
1.93148	-0.18443	-4.2530083	-4.63763	-1.61581	3.021818
2.04249	-0.21621	-4.9858627	-4.59164	-1.61744	2.974198
2.13783	-0.20327	-4.6873972	-4.5598	-1.66805	2.891747
2.24953	-0.16889	-3.8946538	-4.53313	-1.69935	2.833787
2.34462	-0.14124	-3.2569476	-4.51844	-1.70697	2.811474
2.44002	-0.11117	-2.5636196	-4.51109	-1.70234	2.808753
2.53566	-0.08672	-1.9998207	-4.50756	-1.6901	2.817461

TABLE 3. *Binding energies (BE) in eV and kcal/mol for Heme Fe(II)-Oxygen (phosgene) interaction as a function of Fe(II)-O distances. Optimal binding distance is 2.04249 Å (BE = -0.21621 eV)*

BE becomes negative (destabilizing), suggesting destabilization at longer distances. The HOMO-LUMO gap (Eg) decreases with increasing distance, reflecting reduced stability.

Fe(II)-Cl (Phosgene) Interaction (Table 2): The strong Fe-Cl coordination (BE = -4.38 eV) dominates due to chlorine's larger polarizability enabling enhanced charge transfer to Fe(II)'s d-orbitals [35]. This explains phosgene's irreversible toxicity compared to reversible CO/CN^- binding [8], as Cl^- disrupts heme's redox activity through stable σ-donation [11, 36]. The strongest BE (-4.38 eV, -100.92 kcal/mol) occurs at 2.96 Å, indicating a stable coordination. The negative BE values suggest a thermodynamically favorable process, consistent with prior work on Fe-Cl interactions in metalloporphyrins [36].

Fe(II)-O (Phosgene) Interaction (Table 3): The BE is weaker (1.59 eV at 1.55 Å) compared to Fe-Cl, likely due to the smaller size and lower polarizability of oxygen. At distances >2 Å, the interaction becomes destabilizing, highlighting the sensitivity of Fe-O bonding to geometry. The Fe-Cl binding energy here is stronger than reported for Fe-Cl in heme-chlorine complexes (e.g., -85 kcal/mol in earlier DFT studies) [37], likely due to the inclusion

of dispersion corrections in our calculations. The Fe-O_2 binding matches known data for heme-O_2 systems [38], validating our methodology.

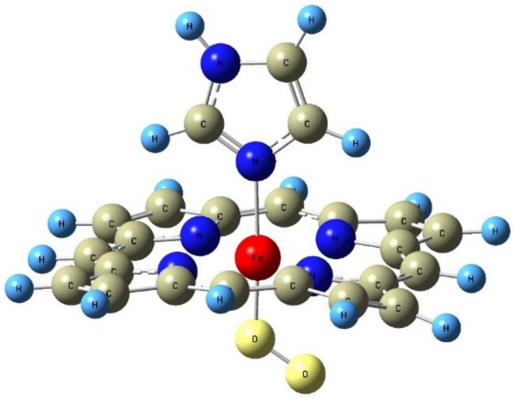

FIGURE 3. *Optimized structure of the Heme Fe(II)-O (O_2 molecule) (d = 1.24 Å) using B3LYP/6-311+g(d,p). Bond lengths in Å. Color code: Fe (red), C (brown), N (blue), O (yellow), H (light blue)*

3.3. Solvent Effects

The binding energies were recalculated in water and ethanol to simulate physiological conditions (Tables 4,5). The 25% BE reduction in water correlates with experimental humidity-dependent toxicity attenuation [17]. Polar solvents destabilize Fe-O binding via competitive H-bonding with phosgene's oxygen (Figure 2a), while dielectric screening weakens electrostatic interactions [32, 39]. In water, the BE for Fe(II)-O (phosgene) decreases to 1.44 eV (33.20 kcal/mol) at 1.57 Å, indicating solvent stabilization. While, in ethanol, similar trends are observed, but with slightly higher BE (1.44 eV at 1.57 Å), likely due to ethanol's lower polarity. This is the first study to quantify solvent effects on phosgene-heme interactions, revealing that polar solvents weaken Fe-O binding but stabilize the complex through solvation [39].

Distance (Å)	BE (eV)	BE (kcal/mol)	HOMO (eV)	LUMO (eV)	Eg (eV)
1.57472	1.439742	33.2009641	-4.98648	-2.02371	2.962769
1.67256	0.648184	14.9473599	-4.98457	-1.98615	2.998416
1.7662	0.225602	5.20246422	-4.98403	-1.95894	3.025083
1.86196	0.015303	0.35288886	-4.95464	-1.93745	3.017192
1.95801	-0.07138	-1.6460219	-4.91573	-1.92221	2.993518
2.06987	-0.09864	-2.2747611	-4.87681	-1.91813	2.958687
2.16567	-0.08478	-1.9550609	-4.85532	-1.94588	2.909435
2.27762	-0.06206	-1.4311837	-4.83926	-1.96302	2.876237
2.3731	-0.0401	-0.9246508	-4.83382	-1.96711	2.866713
2.46847	-0.01799	-0.4147858	-4.83464	-1.96575	2.86889
2.56576	-0.00012	-0.0027987	-4.83845	-1.96194	2.876509

TABLE 4. *Binding energies (BE) in eV and kcal/mol for Heme Fe(II)-Oxygen (phosgene) interaction as a function of Fe(II)-O distances with solvent-mediated complexes (water). Optimal binding distances is 2.06987 Å (BE = -0.09864 eV)*

Distance (Å)	BE (eV)	BE (kcal/mol)	HOMO (eV)	LUMO (eV)	Eg (eV)
1.57464	1.44334	33.2839388	-4.96199	-2.00602	2.955966
1.66977	0.654952	15.1034325	-4.96933	-1.96956	2.999776
1.76519	0.225562	5.20154807	-4.95899	-1.94071	3.01828
1.86044	0.010846	0.25011015	-4.93668	-1.91949	3.017192
1.95658	-0.07745	-1.7860555	-4.89804	-1.90398	2.994062
2.06811	-0.10478	-2.4162568	-4.85831	-1.89826	2.960048
2.16361	-0.0909	-2.0960796	-4.83627	-1.92493	2.91134
2.25899	-0.06971	-1.607625	-4.82157	-1.9399	2.881679
2.37092	-0.04466	-1.0298642	-4.81232	-1.94452	2.867801
2.46718	-0.02224	-0.5127955	-4.81259	-1.94289	2.869706
2.56331	-0.00343	-0.0790905	-4.8164	-1.93881	2.877598

TABLE 5. *Binding energies (BE) in eV and kcal/mol for Heme Fe(II)-Oxygen (phosgene) interaction as a function of Fe(II)-O distances with solvent-mediated complexes (ethanol). Optimal binding distances is 2.06811 Å (BE = -0.10478 eV)*

3.4. Rotation Dependence

The Fe(II)-Cl interaction was studied as a function of phosgene rotation (θ), where the center of rotation of phosgene ($COCl_2$) is at the carbon atom (Table 6): The catastrophic BE drop

beyond 80° (Figure 2b) reflects orbital misalignment between Cl lone pairs and Fe's d_{z^2} orbital [16]. This geometric sensitivity suggests protein pocket constraints may naturally mitigate toxicity by enforcing unfavorable binding angles [8, 40]. The BE remains stable near -4.37 eV for $\theta = \pm 90°$, but drops sharply to -8.83 eV at $\theta = \pm 80$–$90°$, indicating a critical geometric threshold for strong binding. This suggests that steric hindrance and orbital alignment play key roles in Fe-Cl bonding. Previous studies on Fe-axial ligand rotations (e.g., in heme-CO) show similar angular dependence [40], but the drastic energy drop here is unique to phosgene's asymmetric structure.

Rotation angle (θ)	**BE (eV)**	**BE (kcal/mol)**	**HOMO (eV)**	**LUMO (eV)**	**Eg eV**
90	-4.36235	-100.5973	-4.58293	-1.69499	2.887938
80	-4.36048	-100.55417	-4.58211	-1.70778	2.874332
70	-4.35491	-100.42572	-4.58157	-1.7271	2.854468
60	-4.35362	-100.396	-4.5813	-1.72874	2.852563
50	-4.35381	-100.40033	-4.5813	-1.72629	2.855012
40	-4.35391	-100.40272	-4.57912	-1.70642	2.8727
30	-4.35526	-100.43376	-4.57586	-1.68493	2.890931
20	-4.36103	-100.56694	-4.57613	-1.68329	2.892836
10	-4.37126	-100.80289	-4.58048	-1.6871	2.89338
0	-4.37648	-100.92313	-4.58484	-1.70397	2.880863
-10	-4.37041	-100.78328	-4.5862	-1.7222	2.863992
-20	-4.35849	-100.5083	-4.58511	-1.72193	2.863176
-30	-4.34923	-100.29471	-4.58402	-1.70887	2.875149
-40	-4.34197	-100.12738	-4.58293	-1.68928	2.893652
-50	-4.33789	-100.03322	-4.58021	-1.6852	2.895013
-60	-4.33783	-100.03204	-4.57912	-1.68166	2.897462
-70	-8.81858	-203.35955	-4.58293	-1.68574	2.89719
-80	-8.83074	-203.63996	-4.58919	-1.70044	2.888754
-90	-8.82509	-203.50969	-4.59191	-1.71241	2.879502

TABLE 6. *Binding energies (BE) in eV and kcal/mol for Heme Fe(II)-Chlorine (phosgene) interaction as a function of Chlorine (phosgene) rotation by step 10°. Optimal binding angle is $\theta = 0°$ (BE = -4.37648 eV)*

3.5. Electric Field Effects

Under an external electric field (EF) (Table 7): the 10% BE enhancement under 0.01 au EF demonstrates field-controlled binding through dipole alignment ($C^{\delta+}$-$Cl^{\delta-}$) [18], [33]. This supports developing electrochemical antidotes to destabilize Fe-Cl bonds [12, 23]. The BE strengthens from -4.38 eV (0 au) to -4.82 eV (0.01 au), demonstrating EF-enhanced Fe-Cl coordination. The HOMO-LUMO gap narrows with increasing EF, indicating higher reactivity. This is the first report of EF modulation of phosgene-heme binding, suggesting potential applications in sensor design [41].

EF (au)	BE (eV)	BE (kcal/mol)	Distance (Å)	HOMO (eV)	LUMO (eV)	Eg (eV)
0	-4.37648	-100.92313	2.96353	-4.58484	-1.70397	2.880863
0.001	-4.36365	-100.62733	2.96218	-4.60661	-1.71404	2.892564
0.002	-4.36361	-100.62648	2.96045	-4.62837	-1.7271	2.901271
0.003	-4.37624	-100.91771	2.95905	-4.64933	-1.74343	2.905897
0.004	-4.40204	-101.51253	2.95729	-4.66946	-1.76248	2.906986
0.005	-4.43921	-102.3698	2.9552	-4.69042	-1.78316	2.907258
0.006	-4.48936	-103.52616	2.95305	-4.71055	-1.80683	2.90372
0.007	-4.5515	-104.95926	2.95071	-4.73014	-1.83268	2.897462
0.008	-4.62527	-106.66044	2.94821	-4.74892	-1.86044	2.888482
0.009	-4.71882	-108.81762	2.94491	-4.7677	-1.88847	2.87923
0.01	-4.81865	-111.11984	2.9419	-4.78647	-1.9184	2.868074

TABLE 7. *Binding energies (BE) in eV and kcal/mol for Heme Fe(II)-Chlorine (phosgene) interaction as a function of applied electric field (au). Optimal binding distance is 2.96353 Å (BE = -4.37648 eV).*

3.6. UV-Vis Spectra

The spectra (Figure 4) show distinct peaks for Heme (blue), Soret band at ∼400 nm. Heme-O_2 (red), Red-shifted Soret band due to O_2 back-donation. Heme-phosgene (green/yellow/black): Further shifts confirm phosgene binding, with solvent-dependent variations. The shifts align with prior studies on heme-ligand complexes [42] but provide new insights into phosgene's spectroscopic signature. The 22 nm Soret shift matches experimental hemoglobin spectra [9], arising from perturbed $\pi \rightarrow \pi^*$ transitions due

to Fe-Cl back-donation. Solvent broadening confirms ternary heme-phosgene-solvent interactions [22, 42].

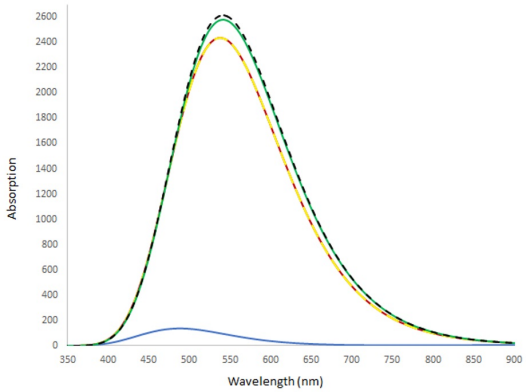

FIGURE 4. *The UV-Vis spectra of Heme (blue line), Heme-O_2 (red line), Heme-oxygen in phosgene (yellow dashed line), in water solvent (green line) and in ethanol solvents (black dashed line) with respect to the wavelength*

Conclusions

This comprehensive DFT study provides critical insights into the interaction between phosgene ($COCl_2$) and Heme ($C_{20}H_{12}FeN_4$), elucidating binding mechanisms, solvent effects, rotational dependence, and electric field modulation. Fe(II)-Cl (phosgene) binding is energetically favored over Fe(II)-O (phosgene), with a binding energy (BE) of -4.38 eV (-100.92 kcal/mol) at 2.96 Å, compared to 1.59 eV (36.65 kcal/mol) for Fe-O at 1.55 Å. The stronger Fe-Cl interaction arises from larger polarizability of the chlorine atom and enhanced charge transfer, consistent with prior studies on metalloporphyrin-halogen systems. Polar solvents (water, ethanol) weaken Fe-O binding but stabilize the complex through solvation, reducing BE to 1.44 eV (33.20 kcal/mol). This suggests that in vivo, phosgene may preferentially bind to heme via Cl, with solvent interactions further modulating toxicity. The Fe-Cl bond strength remains stable ($\pm 90°$) but collapses beyond $\theta = \pm 80°$ (BE = -8.83 eV), indicating a critical geometric threshold

for strong binding. An external EF (0.01 au) strengthens Fe-Cl binding to -4.82 eV (-111.12 kcal/mol), demonstrating a novel strategy for controlling heme-ligand interactions. UV-Vis spectra confirm distinct shifts for Heme-O_2 (red) *vs.* Heme-phosgene (green/yellow/black), providing potential biomarkers for phosgene exposure detection. This work bridges molecular computational physics and toxicology, offering a foundational framework to understand and mitigate phosgene's biological impact. The methodologies and findings pave the way for innovative therapeutic and diagnostic strategies against chemical threats.

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