



Evaluation of the Chemical Stability and Reactivity of 4-nonylphenol Isomers, and Bioaccumulation and Toxicity of their Ethoxylated Molecules and Degradation Products

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ABSTRACT

A reactivity study was conducted on seven isomers of 4-NP using density functional theory at the B3LYP/6-311G (d, p) level. The dipole moment calculation revealed that 4-NP1 is less soluble in aqueous media. Studying frontier molecular orbitals, particularly the energy gap (ΔE), electronegativity (χ), chemical hardness (η), and electrophilic index (ω), provided a clearer picture of the molecular properties. Therefore, the 4-NP1 isomer, which has the highest energy gap between frontier orbitals, is the most stable and least reactive. Analysis of local descriptors and electrostatic potential mapping identified the oxygen atom O₁₁ as the preferred site for electrophilic attacks, and the carbon atom C₃ as the preferred site for nucleophilic attacks, according to *Fukui* indices and dual descriptors. Furthermore, the evaluation of the bioaccumulation, bioconcentration, and biodegradation parameters of the seven 4-NP isomers using the EPI Suite software showed that 4-NP1 is one of the most bioaccumulative isomers and has the longest biodegradation time. Furthermore, it appears that 4-NP1 and the acidic forms of its derivatives present an increased risk of bioaccumulation.

Keywords: Reactivity, 4-nonylphenol, Fukui function, DFT, Bioaccumulation, Toxicity.

INTRODUCTION

Nonionic surfactants are the second most widely used group of surfactants in the world. Among them, polyethoxylated alkylphenols (APEOs) occupy an important place. Their degradation mainly leads to the formation of polyethoxylated

nonylphenols (NPEO, ~80%) and polyethoxylated octylphenols (OPEO, ~20%)¹, compounds widely used in detergents, cosmetics, and pesticides due to their detergent, emulsifying, and solubilizing properties^{2,3,4}. They are the main alkylphenols detected in the environment^{5,6,7}. These degradation products are persistent, bioaccumulative, and



more toxic than their precursors^{8,9,10,11,12}. Due to their estrogenic and toxic effects on aquatic fauna, nonylphenol (NP) and octylphenol (OP) are classified as priority substances by the European Water Framework Directive^{10,13,14}. NP, a major metabolite, is associated with fertility and growth disorders¹⁵. Despite their effects on the environment, studies on NPs and OPs remain limited^{4,10}. Their intensive use and the lack of effective treatment in wastewater treatment plants explain their ubiquitous presence in aquatic environments¹⁶.

This work aims, on the one hand, to evaluate the stability and reactivity of seven isomers of 4-nonylphenol (4-NP) using the DFT method in order to identify the most stable and potentially most persistent isomer, and also to determine their nucleophilic and electrophilic attack sites. On the other hand, it aims to estimate, using the EPI Suite software¹⁷, the bioaccumulation, bioconcentration, and biodegradation parameters of the isomers, as well as the degradation products of ethoxylated nonylphenols.

MATERIAL AND METHODS

Study material

Since 4-nonylphenol encompasses a mixture of branched and substituted nonylphenols in position 4, it represents the vast majority (80%) of nonylphenols (NP) in commercial production. Seven (7) known isomers were selected for this study in order to evaluate their stability and reactivity. These isomers are illustrated in Table 1. This study uses the DFT method with the B3LYP/6-311G(d, p) theoretical level¹⁸. The use of DFT/B3LYP/6-311G(d,p) offers an excellent balance between accuracy, computational costs, and versatility in the study of the chemical reactivity of molecules. The calculation software is Gaussian 09¹⁹ with its Gauss View 05 graphical interface. Graphical and statistical processing was performed using XLSTAT 2016 software to determine the most stable or least reactive isomer.

Starting with the most stable isomer, we identified polyethoxylated nonylphenol. Polyethoxylated nonylphenol undergoes a complex biodegradation process:

Under anaerobic conditions, this biological process leads to the formation of nonylphenol (NP)

and lower-grade ethoxylates (monoethoxylate NP1EO or diethoxylate NP2EO).

Under aerobic conditions, NPEOs are biotransformed into nonylphenoxyacetic acid (NP1EC) or nonylphenoxy-ethoxyacetic acid (NP2EC) and nonylphenol (NP).¹⁶

Also, the most stable isomer and its derivatives (Table 2), calculated using EPI Suite software¹⁷, 4-nonylphenol, allowing comparison of their bioaccumulation, bioconcentration, and biodegradation.

Table 1: Known isomers of nonylphenol (NP)

Code	Structure	Name	Code	Structure	Name
4-NP1		4-(1-éthyl-1,3-triméthylhexyl)-phénol	4-NP5		4-(1-éthyl-1,4-diméthylpentyl)-phénol
4-NP2		4-(1-éthyl-1,3-triméthylhexyl)-phénol	4-NP6		4-(1-éthyl-1,1-n-propylbutyl)-phénol
4-NP3		4-(1-éthyl-1,3-triméthylhexyl)-phénol	4-NP7		4-(1-éthyl-1,3-diméthyl-1-n-propylbutyl)-phénol
4-NP4		4-(1-éthyl-1,3-diméthyl-1,3-diméthylpentyl)-phénol			

Table 2: Nonylphenol ethoxylates and their degradation products

Code	Structure
4-NP1	
4-NP1EO	
4-NP2EO	
4-NP1EC	
4-NP2EC	
4-NP11EO	

Study method

Global Descriptors

Analysis of natural population yielded the atomic charge values. Each NP isomer is optimized using a frequency calculation in vacuum. Next, a single-point calculation that takes into account the effects of solvation (solvent: water; IEFPCM method) on each isomer is performed at the same calculation level. This study retains global stability and reactivity parameters such as the energy gap (ΔE), chemical hardness (η), electrophilicity index (ω), electronegativity (χ), and molecular dipole moment μ (D) are retained for this study. The dipole moment is used to measure the relative solubility of the isomers studied.²⁰ This parameter also characterizes the polarity of a molecule. A molecule is said to be more polar when it has a high dipole moment. The calculations performed make it possible to obtain the energy of the lowest vacant molecular orbital (E_{LUMO}) and the energy of the highest occupied molecular orbital (E_{HOMO}). These energies provide access to different stability and reactivity parameters according to Koopmans approximations²¹. The

energy gap (ΔE) allows the overall chemical stability and reactivity of the different molecules studied to be evaluated through charge transfer. Electronegativity (χ) reflects a molecule's ability to prevent its electrons from escaping. The overall electrophilicity index (ω) characterises the electrophilic power of the molecule. Overall hardness (η) is a measure of the resistance to deformation or polarisation of the electron cloud surrounding atoms, ions or molecules when subjected to a slight disturbance during a chemical reaction. These parameters are calculated using the following equations (1):

$$\Delta E = E_{LUMO} - E_{HOMO}$$

$$\chi = -\mu = -\frac{1}{2}(E_{LUMO} + E_{HOMO})$$

$$\eta = \frac{(E_{LUMO} - E_{HOMO})}{2} \quad (1)$$

$$\omega = \frac{\chi^2}{2\eta\eta}$$

Local and Dual Descriptors

Fukui indices provide information about local reactivity within a molecule. The atom with the highest *Fukui* index is more reactive than the other atoms in the molecule²². These indices offer a qualitative description of the reactivity of the molecule's atoms. The *Fukui* function can successfully predict the relative reactivity of most chemical systems. *Fukui* indices have been determined for the selectivity of electrophilic and nucleophilic atoms in 4-nonylphenol compounds. Ayers and Parr²³ explained that molecules tend to react where the *Fukui* function is highest when attacked by soft reagents, and where it is lower when attacked by hard reagents. Based on the natural atomic charge of optimized compounds in their ground state, the *Fukui* function (f_k^+, f_k^-), local sweetness (S_k^+, S_k^-) and local electrophilicity indices (ω_k^+, ω_k^-)²⁴ have been determined. *Fukui* functions are calculated using equation (2):

The application of finite difference approximations leads to the functions:

$$f_k^+ = [q_k(N+1) - q_k(N)]$$

$$f_k^- = [q_k(N) - q_k(N-1)] \quad (2)$$

Where:

$q_k(N)$: Electron population of the k atom in the neutral molecule.

$q_k(N+1)$: Electronic population of the k atom in the anionic molecule.

$q_k(N-1)$: Electron population of the k atom in the cationic molecule.

The site (atom) for which the value of f_k^{α} is maximal is either a nucleophilic or electrophilic attack center.

The local softness and electrophilicity indices are calculated using:

$$\begin{aligned} S_k^- &= S_f^- \\ S_k^+ &= S_f^+ \\ \omega_k^+ &= f_k^+ \\ \omega_k^- &= f_k^- \end{aligned} \quad (3)$$

The dual descriptor, $\Delta f(r)$, is defined as the difference between the Fukui electrophilic function, $f^+(r)$, and the *Fukui* nucleophilic function, $f^-(r)$. The values of the dual descriptor²⁵ are obtained from equations (4).

$$\Delta f(r) = (f^+(r) - f^-(r)) \quad (4)$$

Descriptors of bioaccumulation, bioconcentration, and biodegradation

Log Kow is an indicator of a substance's lipophilicity, i.e., its tendency to dissolve in fats rather than in water. A high Log Kow (>4) means that the substance is more likely to bioaccumulate in organisms.

The BCF log indicates the concentration of a substance in the tissues of an organism relative to its concentration in water. High values (generally >3) suggest a high potential for bioaccumulation.

Le Log BAF, similaire au Log BCF, évalue la bioaccumulation dans les tissus d'organismes aquatiques. Cela est particulièrement pertinent pour les substances qui se bioaccumulent à travers la chaîne alimentaire.

Biodegradation is the parameter that measures the likelihood of a substance breaking down in the environment. A high likelihood is favorable because it indicates a low persistent risk.

RESULTS AND DISCUSSION

Reactivity descriptors

The study of the overall reactivity of isomers is based on calculating overall indices derived from electronic properties. These indices show very similar values for certain isomers. In the absence of a standard, the study of relative chemical stability is based on a qualitative comparison of the calculated overall indices.

The values of the energy descriptors of the 4-NP isomers are shown in Table 3.

Descriptors of overall reactivity and dipole moment

Dipole moment of compounds

The dipole moment, the value of which is critical for predicting solubility in aqueous media, ranges from 1.882 Debye (isomers 4-NP1 and 4-NP7) to 2.140 Debye (isomer 4-NP4), according to the data in Table 3.

The order of decreasing polarity and solubility is as follows:



Global reactivity descriptors

The reactivity and stability of the compounds are directly related to their calculated energy gaps. Compound 4-NP1, with the maximum energy gap ($\Delta E = 5.689$ eV), is therefore characterized as the most stable and least reactive. Conversely, the minimum energy gap ($\Delta E = 5.682$ eV) was observed for compounds 4-NP7 and 4-NP4, indicating they are less stable and more reactive. Thus, the following sequence can be established in descending order of stability: $4\text{-NP1} > 4\text{-NP3} \cong 4\text{-NP5} > 4\text{-NP6} > 4\text{-NP2} > 4\text{-NP4} \cong 4\text{-NP7}$

In terms of chemical hardness (η), compound 4-NP1 has the highest value ($\eta = 2.845$ eV), indicating that it is the hardest of the compounds. In terms of the electrophilic index (ω), compound 4-NP6 has the lowest value ($\omega = 3.900$ eV). This value indicates that this compound is less able to accept electrons. The slightly higher electrophilic indices of 4-NP2 and 4-NP4 suggest increased reactivity to electron attacks. These results confirm a moderate influence of the isomeric structure on the reactivity and polarity of 4-NP.

Table 3: Frontier Molecular Orbital Energies and Energy Gap (ΔE), in eV, for Compound 4-NP (Calculated at the B3LYP/6-311G (d,p) Level)

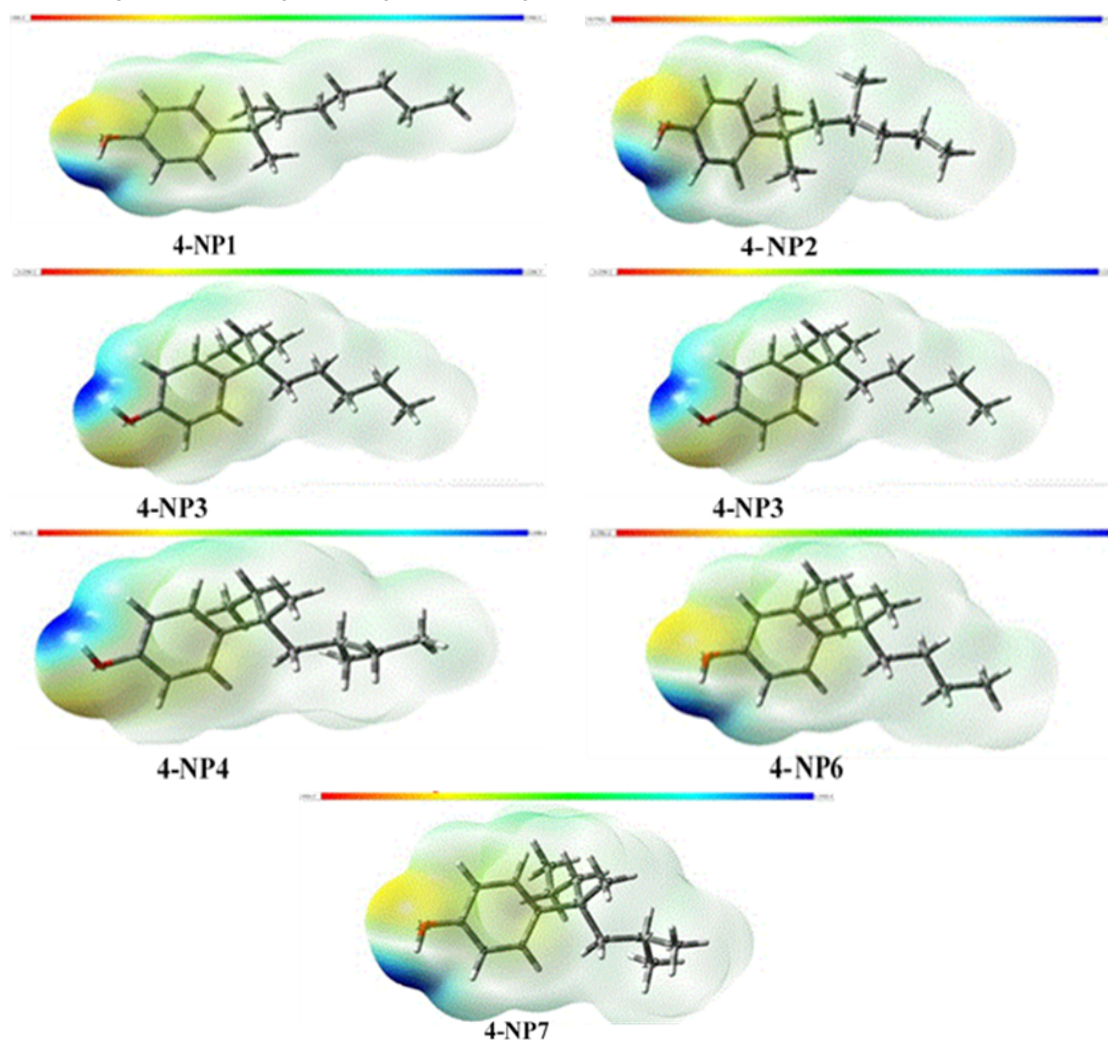
Molecules	E(HO) eV	E(BV) eV	ΔE (eV)	χ (eV)	μ (eV)	η (eV)	ω (eV)	μ (D)
4-NP 1	-6.178	-0.489	5.689	3.334	-3.334	2.845	3.907	1.961
4-NP 2	-6.181	-0.495	5.686	3.338	-3.338	2.843	3.919	1.982
4-NP 3	-6.176	-0.488	5.687	3.332	-3.332	2.844	3.904	2.121
4-NP 4	-6.178	-0.496	5.682	3.337	-3.337	2.841	3.919	2.140
4-NP 5	-6.177	-0.489	5.687	3.333	-3.333	2.844	3.906	1.990
4-NP 6	-6.174	-0.487	5.687	3.330	-3.330	2.843	3.900	2.045
4-NP 7	-6.175	-0.494	5.682	3.334	-3.334	2.841	3.914	1.882

Local reactivity descriptors

Electrostatic potentials, molecules, and Fukui functions

A color scale is employed to visualize the surface electrostatic potential areas, where the potential progressively increases from red (indicating the most negative regions) through

orange, yellow, and green, to blue (indicating the most positive regions)²⁶. The electrostatic potential (ESP) surfaces for the molecules investigated were generated using the DFT/B3LYP/6-311G (d,p) level of optimization. The resulting surfaces, calculated with Gaussian 09²⁷, are displayed in Figure 1.


Fig. 1. Surface of molecular electrostatic potentials of 4-NP isomers

Using Equations (2), (3), and (4), we determined the local and dual reactivity descriptors for each compound to predict precise electrophilic

and nucleophilic attack sites. These descriptors, calculated solely for the heavy atoms, are grouped in Tables 4–10.

Table 4: Reactivity descriptors for compound 4-NP 1. Values were calculated using natural population analysis (NPA) at the B3LYP/6-311G (d,p) level

Atomes	Descripteurs locaux				Descripteurs duals				
	f+	f-	s+	s-	ω+	ω-	Δf	Δs	Δω
C1	-0.163	0.135	-0.057	0.047	-0.636	0.527	-0.297	-0.105	-1.162
C2	-0.198	0.261	-0.069	0.092	-0.772	1.019	-0.458	-0.161	-1.791
C3	0.169	0.031	0.059	0.011	0.659	0.123	0.137	0.0482	0.536
C4	-0.184	0.232	-0.065	0.081	-0.718	0.905	-0.415	-0.146	-1.623
C5	-0.177	0.132	-0.062	0.046	-0.691	0.515	-0.309	-0.108	-1.206
C6	0.012	0.301	0.004	0.106	0.0437	1.176	-0.290	-0.102	-1.132
O11	-0.353	0.536	-0.124	0.189	-1.379	2.096	-0.889	-0.313	-3.475
C13	-0.054	0.044	-0.019	0.015	-0.212	0.170	-0.098	-0.034	-0.382
C14	-0.344	0.348	-0.121	0.122	-1.345	1.360	-0.692	-0.243	-2.704
C18	-0.352	0.342	-0.124	0.120	-1.377	1.337	-0.694	-0.244	-2.713
C22	-0.226	0.235	-0.079	0.083	-0.883	0.920	-0.461	-0.162	-1.803
C25	-0.237	0.241	-0.083	0.085	-0.924	0.942	-0.478	-0.168	-1.866
C28	-0.233	0.235	-0.082	0.083	-0.912	0.918	-0.468	-0.165	-1.830
C31	-0.235	0.236	-0.083	0.083	-0.917	0.921	-0.470	-0.165	-1.838
C34	-0.240	0.240	-0.084	0.084	-0.939	0.937	-0.480	-0.169	-1.876
C37	-0.349	0.349	-0.123	0.1227	-1.364	1.364	-0.698	-0.245	-2.728

Table 5: Reactivity descriptors for compound 4-NP 2. Values were calculated using natural population analysis (NPA) at the B3LYP/6-311G (d,p) level

Atomes	f+	f-	s+	s-	ω+	ω-	Δf	Δs	Δω
C1	-0.161	0.134	-0.057	0.047	-0.631	0.524	-0.295	-0.104	-1.154
C2	-0.199	0.263	-0.070	0.092	-0.778	1.030	-0.461	-0.162	-1.808
C3	0.169	0.031	0.059	0.011	0.663	0.120	0.139	0.049	0.543
C4	-0.184	0.229	-0.065	0.080	-0.719	0.896	-0.412	-0.145	-1.615
C5	-0.178	0.133	-0.063	0.047	-0.696	0.520	-0.310	-0.109	-1.216
C6	0.011	0.301	0.004	0.106	0.041	1.181	-0.291	-0.102	-1.140
O11	-0.353	0.535	-0.124	0.188	-1.385	2.098	-0.889	-0.313	-3.483
C13	-0.053	0.042	-0.019	0.015	-0.209	0.166	-0.096	-0.034	-0.375
C14	-0.220	0.231	-0.077	0.081	-0.861	0.906	-0.451	-0.159	-1.767
C17	-0.142	0.149	-0.050	0.052	-0.558	0.584	-0.291	-0.103	-1.142
C19	-0.229	0.229	-0.080	0.081	-0.897	0.899	-0.458	-0.161	-1.796
C22	-0.240	0.241	-0.084	0.085	-0.939	0.943	-0.480	-0.169	-1.882
C25	-0.349	0.349	-0.123	0.123	-1.367	1.368	-0.698	-0.245	-2.735
C29	-0.344	0.349	-0.121	0.123	-1.349	1.366	-0.693	-0.244	-2.715
C33	-0.352	0.341	-0.124	0.120	-1.378	1.337	-0.693	-0.244	-2.715
C37	-0.345	0.344	-0.122	0.121	-1.354	1.349	-0.690	-0.243	-2.703

Table 6: Reactivity descriptors for compound 4-NP 3. Values were calculated using natural population analysis (NPA) at the B3LYP/6-311G (d,p) level

Atomes	f+	f-	s+	s-	ω+	ω-	Δf	Δs	Δω
C1	-0.182	0.146	-0.064	0.0512	-0.711	0.568	-0.328	-0.115	-1.280
C2	-0.189	0.230	-0.066	0.081	-0.736	0.898	-0.419	-0.147	-1.635
C3	0.169	0.032	0.059	0.011	0.659	0.124	0.137	0.048	0.535
C4	-0.191	0.267	-0.067	0.094	-0.747	1.041	-0.458	-0.161	-1.788
C5	-0.158	0.118	-0.056	0.042	-0.617	0.462	-0.276	-0.097	-1.078
C6	0.010	0.302	0.004	0.106	0.039	1.180	-0.292	-0.103	-1.140
O11	-0.353	0.538	-0.124	0.189	-1.380	2.100	-0.891	-0.313	-3.480
C13	-0.050	0.038	-0.018	0.013	-0.197	0.148	-0.088	-0.031	-0.345
C14	-0.235	0.227	-0.083	0.080	-0.918	0.885	-0.462	-0.162	-1.804
C17	-0.234	0.233	-0.082	0.082	-0.914	0.910	-0.467	-0.164	-1.823
C20	-0.234	0.233	-0.082	0.082	-0.913	0.908	-0.466	-0.164	-1.821
C23	-0.239	0.238	-0.084	0.084	-0.932	0.931	-0.477	-0.168	-1.863
C26	-0.350	0.349	-0.123	0.123	-1.365	1.364	-0.699	-0.246	-2.729
C30	-0.233	0.241	-0.082	0.085	-0.911	0.940	-0.474	-0.167	-1.851
C33	-0.353	0.351	-0.124	0.123	-1.377	1.370	-0.704	-0.247	-2.747
C37	-0.341	0.349	-0.120	0.123	-1.333	1.364	-0.691	-0.243	-2.697

Table 7: Reactivity descriptors for compound 4-NP 4. Values were calculated using natural population analysis (NPA) at the B3LYP/6-31+G (d,p) level

Atomes	f+	f-	s+	s-	ω+	ω-	Δf	Δs	Δω
C1	-0.180	0.145	-0.064	0.051	-0.707	0.569	-0.326	-0.115	-1.276
C2	-0.189	0.231	-0.066	0.081	-0.740	0.905	-0.420	-0.148	-1.645
C3	0.169	0.032	0.059	0.011	0.662	0.125	0.137	0.0482	0.537
C4	-0.191	0.266	-0.067	0.094	-0.749	1.042	-0.457	-0.161	-1.792
C5	-0.158	0.118	-0.056	0.042	-0.619	0.463	-0.276	-0.097	-1.081
C6	0.010	0.303	0.003	0.107	0.038	1.186	-0.293	-0.103	-1.149
O11	-0.354	0.538	-0.125	0.189	-1.387	2.109	-0.892	-0.314	-3.495
C13	-0.049	0.037	-0.017	0.013	-0.193	0.144	-0.086	-0.030	-0.336
C14	-0.230	0.221	-0.081	0.078	-0.900	0.867	-0.451	-0.159	-1.767
C17	-0.141	0.142	-0.050	0.050	-0.553	0.556	-0.283	-0.100	-1.109
C19	-0.234	0.233	-0.082	0.082	-0.918	0.914	-0.468	-0.165	-1.833
C22	-0.350	0.350	-0.123	0.123	-1.372	1.370	-0.700	-0.246	-2.743
C26	-0.232	0.241	-0.082	0.085	-0.910	0.944	-0.473	-0.167	-1.854
C29	-0.352	0.350	-0.124	0.123	-1.381	1.372	-0.703	-0.247	-2.754
C33	-0.342	0.349	-0.120	0.123	-1.341	1.366	-0.691	-0.243	-2.707
C37	-0.345	0.343	-0.121	0.121	-1.350	1.346	-0.688	-0.242	-2.696

Table 8: Reactivity descriptors for compound 4-NP 5. Values were calculated using natural population analysis (NPA) at the B3LYP/6-311G(d,p) level

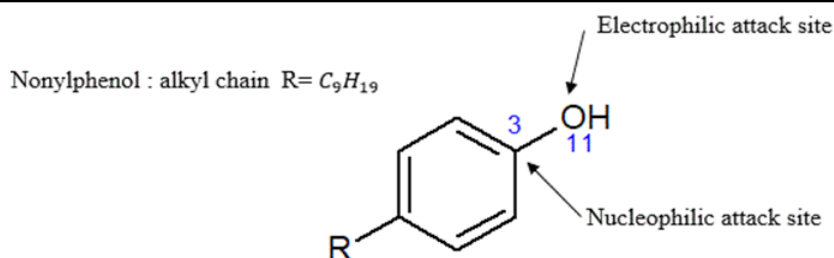
Atomes	f+	f-	s+	s-	ω+	ω-	Δf	Δs	Δω
C1	-0.181	0.145	-0.064	0.051	-0.515	0.414	-0.327	-0.115	-0.929
C2	-0.189	0.230	-0.066	0.081	-0.537	0.654	-0.419	-0.147	-1.191
C3	0.1688	0.032	0.059	0.011	0.480	0.090	0.137	0.048	0.390
C4	-0.191	0.267	-0.067	0.094	-0.543	0.758	-0.458	-0.161	-1.301
C5	-0.158	0.118	-0.055	0.041	-0.448	0.335	-0.275	-0.097	-0.783
C6	0.010	0.302	0.004	0.106	0.028	0.859	-0.292	-0.103	-0.830
O11	-0.353	0.538	-0.124	0.189	-1.005	1.530	-0.891	-0.313	-2.535
C13	-0.050	0.038	-0.018	0.013	-0.142	0.107	-0.088	-0.031	-0.249
C14	-0.236	0.228	-0.083	0.080	-0.671	0.648	-0.464	-0.163	-1.319
C17	-0.230	0.229	-0.081	0.081	-0.655	0.651	-0.459	-0.161	-1.306
C20	-0.142	0.142	-0.050	0.050	-0.405	0.405	-0.285	-0.100	-0.810
C21	-0.344	0.344	-0.121	0.121	-0.980	0.978	-0.688	-0.242	-1.958
C25	-0.233	0.241	-0.082	0.085	-0.664	0.684	-0.474	-0.167	-1.348
C28	-0.352	0.351	-0.124	0.123	-1.002	0.998	-0.703	-0.247	-2.000
C32	-0.341	0.349	-0.120	0.123	-0.971	0.993	-0.690	-0.243	-1.964

Table 9: Reactivity descriptors for compound 4-NP 6. Values were calculated using natural population analysis (NPA) at the B3LYP/6-311G(d,p) level

Atomes	f+	f-	s+	s-	ω+	ω-	Δf	Δs	Δω
C1	-0.180	0.131	-0.063	0.046	-0.702	0.512	-0.311	-0.109	-1.214
C2	-0.182	0.230	-0.064	0.081	-0.710	0.898	-0.412	-0.145	-1.608
C3	0.169	0.032	0.059	0.011	0.657	0.124	0.137	0.048	0.534
C4	-0.199	0.265	-0.070	0.093	-0.774	1.032	-0.463	-0.163	-1.806
C5	-0.160	0.133	-0.056	0.047	-0.622	0.519	-0.293	-0.103	-1.141
C6	0.011	0.302	0.004	0.106	0.042	1.177	-0.291	-0.102	-1.135
O11	-0.354	0.537	-0.124	0.190	-1.379	2.096	-0.891	-0.313	-3.475
C13	-0.050	0.038	-0.018	0.013	-0.195	0.147	-0.088	-0.031	-0.342
C14	-0.235	0.227	-0.083	0.080	-0.917	0.884	-0.462	-0.162	-1.802
C17	-0.235	0.234	-0.083	0.082	-0.916	0.911	-0.468	-0.165	-1.827
C20	-0.239	0.237	-0.084	0.083	-0.930	0.925	-0.476	-0.167	-1.855
C23	-0.349	0.349	-0.123	0.123	-1.363	1.361	-0.698	-0.246	-2.724
C27	-0.228	0.236	-0.080	0.083	-0.890	0.921	-0.464	-0.163	-1.811
C30	-0.242	0.242	-0.085	0.085	-0.945	0.944	-0.484	-0.170	-1.889
C33	-0.349	0.348	-0.123	0.122	-1.363	1.357	-0.697	-0.245	-2.720
C37	-0.341	0.350	-0.120	0.123	-1.331	1.364	-0.691	-0.243	-2.695

Table 10: Reactivity descriptors for compound 4-NP 7. Values were calculated using natural population analysis (NPA) at the B3LYP/6-311G (d,p) level

Atomes	f+	f-	s+	s-	ω+	ω-	Δf	Δs	Δω
C1	-0.179	0.131	-0.063	0.046	-0.699	0.513	-0.310	-0.109	-1.212
C2	-0.182	0.231	-0.064	0.081	-0.713	0.903	-0.413	-0.145	-1.616
C3	0.168	0.032	0.059	0.011	0.658	0.124	0.137	0.048	0.534
C4	-0.198	0.264	-0.070	0.093	-0.775	1.035	-0.462	-0.163	-1.810
C5	-0.159	0.133	-0.056	0.047	-0.624	0.520	-0.292	-0.103	-1.144
C6	0.010	0.303	0.004	0.106	0.039	1.184	-0.292	-0.103	-1.145
O11	-0.354	0.538	-0.125	0.189	-1.385	2.104	-0.891	-0.314	-3.489
C13	-0.049	0.037	-0.017	0.013	-0.191	0.144	-0.086	-0.030	-0.335
C14	-0.231	0.222	-0.081	0.078	-0.903	0.868	-0.452	-0.159	-1.770
C17	-0.146	0.147	-0.051	0.052	-0.571	0.573	-0.292	-0.103	-1.144
C19	-0.344	0.342	-0.121	0.121	-1.345	1.340	-0.686	-0.242	-2.685
C23	-0.228	0.236	-0.080	0.083	-0.890	0.923	-0.463	-0.163	-1.813
C26	-0.241	0.242	-0.085	0.085	-0.945	0.948	-0.484	-0.170	-1.893
C29	-0.350	0.348	-0.123	0.123	-1.368	1.362	-0.698	-0.246	-2.731
C33	-0.342	0.349	-0.120	0.123	-1.338	1.366	-0.691	-0.243	-2.703
C37	-0.344	0.343	-0.121	0.121	-1.348	1.343	-0.688	-0.242	-2.691


Fig. 2. Similar regioselectivity for all isomers

The local descriptors displayed in Tables 4–10 consistently show that the carbon atom C₃ is the site most susceptible to nucleophilic attack, whereas the oxygen atom O₁₁ is the main site for electrophilic attack.

At the dual descriptor level, they were used as ideal descriptors of the regioselectivity of the different attack sites. Analysis of the dual descriptors (calculated at the B3LYP/6-311G (d,p) level) corroborates the local descriptor findings: the oxygen atom O₁₁ is confirmed as the preferred electrophilic attack site, and the carbon

atom C₃ as the nucleophilic attack site. Crucially, the preferred sites (O₁₁ and C₃) remain consistent across all studied 4-NP isomers, as illustrated in Figure 2.

Determination of the bioaccumulation and toxicity of known isomers of 4-nonylphenol

The structural characterization of 4-NP isomers has been of great interest and has enabled the identification of these bioaccumulative and toxic isomers. The parameters relating to the descriptors of bioaccumulation, bioconcentration, and biodegradation are presented in Table 11.

Table 11: Descriptors of bioaccumulation, bioconcentration, and biodegradation of 4-NP isomers, calculated using EPI Suite software

Molecules	Bioaccumulation and Bioconcentration				Time required (weeks)	Biodegradation anaerobic
	Log Kow	LogBCF	LogBAF	Probability		
4-NP1	5.88	3.545	3.122	0.6829	2.8548	-0.2256
4-NP2	5.80	3.497	3.047	0.5745	2.5565	-0.2053
4-NP3	5.88	3.545	3.122	0.6829	2.8548	-0.2256
4-NP4	5.80	3.497	3.047	0.5745	2.5565	-0.2053
4-NP5	5.80	3.497	3.047	0.5745	2.5565	-0.2053
4-NP6	5.88	3.545	3.122	0.6829	2.8548	-0.2256
4-NP7	5.80	3.497	3.047	0.5745	2.5565	-0.2053

Log Kow

Log Kow values range from 5.80 to 5.88. These values indicate that all molecules are lipophilic, meaning they have a strong affinity for lipids relative to water. This suggests a high potential for bioaccumulation in aquatic organisms, which is of concern for environmental impacts.

Log BCF

Log BCF values range from 3.497 to 3.545. These results show that certain molecules such as 4-NP1, 4-NP3, and 4-NP6 have a higher bioconcentration potential. This means that they can accumulate in the tissues of aquatic organisms, thereby increasing the risk of toxicity within food chains.

Log BAF

The Log BAF values are similar, indicating consistent behavior in terms of bioconcentration. The proximity of the values suggests that all molecules pose a risk of bioconcentration, although some, such as 4-NP1, 4-NP3, and 4-NP6, show slightly higher potential, which may increase the overall risk.

Probability of Biodegradation

This parameter measures the likelihood that a substance will break down in the environment. A high probability is favorable because it indicates a low persistent risk. The biodegradation probabilities range from 0.5745 to 0.6829. The molecules 4-NP1,

4-NP3, and 4-NP6 have higher values, indicating that they are more likely to degrade in the environment. In contrast, 4-NP2, 4-NP4, 4-NP5, and 4-NP7 show less favorable biodegradability, suggesting that they may persist longer in the environment.

Time Required for Anaerobic Biodegradation

This parameter indicates the time it takes for a substance to decompose in the absence of oxygen. Shorter times are generally desirable. The times required for anaerobic biodegradation range from 2.5565 to 2.8548 weeks. Shorter times are generally preferable, as they indicate faster degradation. The molecules 4-NP1, 4-NP3, and 4-NP6 have longer times, suggesting that they may decompose less efficiently under anaerobic conditions.

Comparison of bioaccumulation, bioconcentration, and biodegradation of 4-NP1 molecules and their derivatives.

Based on previous studies of reactivity and calculations of bioaccumulation, bioconcentration, and biodegradation, it appears that 4-NP1 is the most stable isomer and is one of the three isomers with the highest potential for bioaccumulation and the longest time required for anaerobic biodegradation. Its high lipophilicity combined with its stability promotes its bioaccumulation in aquatic organisms, causing it to move up the food chain. Hence, the choice of the 4-NP1 isomer.

Table 12: Descriptors of bioaccumulation, bioconcentration, and biodegradation of 4-NP1 molecules and their derivatives, calculated using EPI Suite software

Molecules	Bioaccumulation and Bioconcentration				Biodegradation	
	Log Kow	LogBCF	LogBAF	Probability	Time Required (weeks)	anaerobic
4-NP1	5.88	3.545	3.122	0.6829	2.8548	-0.2256
4-NPEO11	2.72	1.207	1.401	0.4219	3.0555	-1.9963
4-NPEC1	5.69	1.000	4.083	0.6585	2.9767	0.0844
4-NPEO1	5.47	1.643	3.261	0.8368	2.8029	0.0564
4-NPEC2	5.42	1.000	3.412	0.3758	2.8706	-0.1209
4-NPEO2	5.19	1.462	3.037	0.4685	2.6969	-0.1489

Analysis of bioaccumulation and biodegradation parameters reveals significant differences between the compounds studied.

Log Kow

The Log Kow values, which indicate hydrophobicity, range from 2.72 to 5.88, reflecting a general tendency toward lipophilicity, which is particularly pronounced for 4-NP1 (Log Kow = 5.88) and 4-NPEC1 (Log Kow =

5.69). These high values suggest a strong affinity for lipid-rich biological environments, which promotes their bioaccumulation and bioconcentration in aquatic organisms. This result is consistent with observations made on branched nonylphenols²⁸. Furthermore, the high values observed in this study suggest a potential for trophic accumulation, a phenomenon already widely documented for nonylphenols and their degraded ethoxylates²⁹.

Log BCF and Log BAF

The Log BCF and Log BAF values confirm this trend. The molecules 4-NP1, 4-NPEC1, and 4-NPEO1 have Log BAF values >3, indicating a high potential for biomagnification in food chains. This statement is consistent with the fact that studies have shown very high BCFs for 4-NP in aquatic organisms such as algae. Par exemple, Ho *et al.*,³⁰ reported a BCF of 1.2×10^3 in *Chlorella vulgaris*. Conversely, derivatives such as 4-NPEO11 and 4-NPEO2 show lower values (Log BAF between 1.401 and 3.037), suggesting a more moderate risk of bioaccumulation, probably related to their greater water solubility due to the presence of longer ethoxylated chains. This hypothesis is supported by toxicokinetic and persistence assessments, which conclude that ethoxylation tends to decrease the potential for bioaccumulation²⁸.

Probability of biodegradation

The probabilities obtained (from 0.37 to 0.84) show variable degradability depending on the structure. 4-NPEO1 (probability = 0.8368) appears to be the most readily biodegradable, while 4-NPEC2 and 4-NPEO11 have the lowest values, 0.3758 and 0.4219 respectively, indicating increased persistence in the environment. Biodegradation times, ranging from 2.7 to 3.0 weeks, confirm that the decomposition of these compounds is slow, reflecting limited biodegradation, particularly under anaerobic conditions, where the negative values observed (-1.99 for 4-NPEO11) suggest a virtual absence of degradation. Overall, the results highlight that 4-nonylphenol derivatives have significant ecotoxicological potential due to their high bioaccumulation potential and low biodegradability, particularly for the most hydrophobic compounds (4-NP1, 4-NPEC1). These characteristics confirm their environmental persistence and justify regulatory vigilance regarding their use and release into aquatic environments.

CONCLUSION

In-depth theoretical analysis of 4-nonylphenol isomers clearly highlights the decisive influence of isomeric configuration on their structural, electronic, and environmental properties. Overall reactivity descriptors indicate that 4-NP1 has increased electronic stability and marked hydrophobicity, while 4-NP4, characterized by higher polarity, shows greater affinity for hydrophilic environments. Furthermore, the study of local and double descriptors reveals remarkably consistent regioselectivity, systematically identifying carbon C₃ as the preferred site of nucleophilic attack and oxygen atom O₁₁ as the main electrophilic center. From an environmental perspective, the results highlight differentiated risk profiles, including a high potential for bioaccumulation and increased persistence for the most hydrophobic isomers, particularly under anaerobic conditions. Taken together, these observations demonstrate the relevance of an integrated approach combining theoretical chemistry and environmental assessment to anticipate the fate of persistent organic pollutants and guide management strategies aimed at mitigating the ecological impact of 4-nonylphenol derivatives.

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Conflict of Interest

The authors declares that they have no conflict of interest.

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