

Appendix A: Generated Explanations from XpertAI and ChatGPT (baseline)

Case study 1. Understanding presence of open metal sites in MOFs:

[XpertAI Explanation]

Features Identified by XAI Analysis

- Metals fraction
- Density of solid
- Average Cationic Radius

Metals Fraction:

Explanation: The feature "metals fraction" relate to the proportion of metal ions in the MOF structure that are not fully coordinated, potentially indicating the presence of open metal sites (OMS). A higher fraction of uncoordinated metal ions might suggest a greater number of OMS, which are crucial for adsorption and catalytic applications in MOFs.

Scientific Evidence: The documents discuss the importance of maintaining the structural integrity of MOFs while modifying metal ions to create OMS (Kökçam-Demir et al., 2020). This implies that the fraction of uncoordinated metal ions is a critical factor in the presence of OMS.

Hypothesis: A higher "metals fraction" could correlate with an increased presence of OMS, as it may indicate more metal ions are available to form these sites.

Density of Solid:

Explanation: The "density of solid" feature could influence the presence of OMS by affecting the packing and porosity of the MOF structure. A lower density might suggest a more open framework, potentially allowing for more OMS.

Scientific Evidence: The documents highlight the role of density in differentiating MOF structures and its impact on adsorption properties (Chung et al., 2019). This suggests that density is a significant factor in the structural characteristics of MOFs, which could relate to the presence of OMS.

Hypothesis: A lower density of solid might be associated with a higher presence of OMS due to increased porosity and structural openness.

Average Cationic Radius:

Explanation: The "average cationic radius" could affect the presence of OMS by influencing the coordination environment and the ability of metal ions to form unsaturated sites. Larger cations might create more space for OMS.

Scientific Evidence: The documents discuss the influence of ionic radius on the binding strength of gases in MOFs, suggesting that cation size affects the coordination environment (Zhou et al., 2008).

Hypothesis: A larger average cationic radius might correlate with a higher presence of OMS, as it could facilitate the formation of unsaturated coordination sites.

Summary

The features identified by the XAI analysis—metals fraction zero, density of solid, and average cationic radius—are

potentially related to the presence of open metal sites (OMS) in metal-organic frameworks (MOFs). The "metals fraction zero" feature may indicate the proportion of uncoordinated metal ions, which are directly related to OMS. The "density of solid" could influence the structural openness and porosity of MOFs, affecting the availability of OMS. Lastly, the "average cationic radius" might impact the coordination environment, with larger cations potentially facilitating the formation of OMS. While the documents do not explicitly state these relationships, they provide insights into the structural and chemical factors influencing OMS in MOFs, allowing for the generation of hypotheses based on the provided information (Kökçam-Demir et al., 2020; Chung et al., 2019; Zhou et al., 2008).

References

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[ChatGPT Explanation]

Features Identified by ChatGPT

- Metal Ion Coordination Environment
- Ligand Structure and Functional Groups
- Synthesis Conditions
- Post-Synthetic Modifications
- Solvent Removal Techniques
- Framework Topology
- Metal-Ligand Bond Strength
- Guest Molecule Presence

Metal Ion Coordination Environment:

Explanation: The coordination environment of the metal ion is crucial in determining the presence of open metal sites. If the metal ion is under-coordinated, it can result in open metal sites. For example, a metal ion that typically prefers a coordination number of six but is only coordinated by four ligands will have two open coordination sites.

Hypothesis: The coordination number and geometry of the metal ion directly influence the likelihood of open metal sites. Metal ions with flexible coordination environments are more likely to exhibit open metal sites.

Ligand Structure and Functional Groups:

Explanation: The structure and functional groups of the ligands can influence the coordination environment of the metal ions. Bulky ligands or those with steric hindrance can prevent full coordination of the metal ion, leading to open metal sites. Additionally, ligands with specific functional groups can either donate or withdraw electron density, affecting the metal's coordination.

Hypothesis: Ligands with bulky or sterically hindered structures, or those with electron-withdrawing groups, are more likely to result in open metal sites due to incomplete coordination of the metal ions.

Synthesis Conditions:

Explanation: The conditions under which MOFs are synthesized, such as temperature, pH, and solvent, can affect the formation of open metal sites. High temperatures or specific pH levels can lead to partial coordination of metal ions, while certain solvents can stabilize under-coordinated metal sites.

Hypothesis: Specific synthesis conditions, such as elevated temperatures and particular pH levels, promote the formation of open metal sites by influencing the coordination dynamics of the metal ions.

Post-Synthetic Modifications:

Explanation: Post-synthetic modifications, such as ligand exchange or metal ion substitution, can introduce or expose open metal sites. These modifications can alter the coordination environment of the metal ions, leading to the creation of open sites.

Hypothesis: Post-synthetic modifications that involve ligand exchange or metal ion substitution are likely to increase the presence of open metal sites by altering the coordination environment.

Solvent Removal Techniques:

Explanation: The method used to remove solvents from the MOF structure can impact the presence of open metal sites. Gentle solvent removal techniques can preserve open metal sites, while harsh conditions might lead to collapse or re-coordination of the metal ions.

Hypothesis: Gentle solvent removal techniques are more likely to preserve open metal sites, whereas harsh conditions may reduce their presence by causing structural collapse or re-coordination.

Framework Topology:

Explanation: The overall topology of the MOF framework can influence the accessibility and presence of open metal sites. Certain topologies may inherently favor the formation of open metal sites due to their geometric arrangement.

Hypothesis: MOF frameworks with topologies that create spacious and accessible environments are more likely to exhibit open metal sites.

Metal-Ligand Bond Strength:

Explanation: The strength of the metal-ligand bond can affect the stability of open metal sites. Weaker bonds may lead to more dynamic coordination environments, increasing the likelihood of open metal sites.

Hypothesis: Weaker metal-ligand bonds are associated with a higher likelihood of open metal sites due to the increased flexibility in coordination.

Guest Molecule Presence:

Explanation: The presence of guest molecules within the MOF can influence the coordination environment of the metal ions. Guest molecules can either block or stabilize open metal sites, depending on their size and interaction with the framework.

Hypothesis: The presence of guest molecules that do not strongly interact with the metal ions is more likely to preserve open

metal sites, while those that interact strongly may block or stabilize these sites.

Summary

The presence of open metal sites in Metal-Organic Frameworks (MOFs) is influenced by a variety of molecular features. The coordination environment of the metal ion is a primary determinant, with under-coordinated metal ions leading to open sites. Ligand structure and functional groups also play a significant role, as bulky or electron-withdrawing ligands can prevent full coordination. Synthesis conditions, such as temperature and pH, can affect the formation of open metal sites by influencing the coordination dynamics. Post-synthetic modifications, solvent removal techniques, and the overall framework topology further contribute to the presence of open metal sites. Additionally, the strength of the metal-ligand bond and the presence of guest molecules within the MOF can either promote or inhibit the formation of open metal sites. Understanding these relationships is crucial for the design and synthesis of MOFs with desired properties, particularly for applications requiring accessible metal sites.

References

1. Furukawa, H., Cordova, K. E., O'Keeffe, M., & Yaghi, O. M. (2013). The chemistry and applications of metal-organic frameworks. *Science*, 341(6149), 1230444.
2. Kitagawa, S., Kitaura, R., & Noro, S. (2004). Functional porous coordination polymers. *Angewandte Chemie International Edition*, 43(18), 2334-2375.
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Case study 2. Understanding pore limiting diameter in MOFs:

[XpertAT Explanation]

Features Identified by XAI Analysis

- Volume per Atom
- Symmetry Function G1
- Unoccupied Energy Levels Near the Conduction Band Minimum

Volume per Atom:

Explanation: The volume per atom in a material can influence the pore limiting diameter (PLD) in metal-organic frameworks (MOFs) by affecting the overall density and packing of the framework. A larger volume per atom might suggest a more open structure, potentially leading to larger pore sizes, while a smaller volume per atom could indicate tighter packing and smaller pores.

Scientific Evidence: The documents discuss the importance of crystal density as a descriptor for MOF structures, which is related to the volume per atom. Variations in atomic packing, which are influenced by the volume per atom, can lead to different structures and pore sizes (Chung et al., 2019).

Hypothesis: A higher volume per atom in MOFs may correlate with larger pore limiting diameters due to less dense atomic packing, allowing for larger channels within the framework.

Symmetry Function G1:

Explanation: Symmetry functions, such as G1, are often used in computational chemistry to describe the local environment around atoms. While the documents do not explicitly mention Symmetry Function G1, symmetry in general can influence the arrangement of atoms and thus the pore structure in MOFs.

Scientific Evidence: An explicit relationship between Symmetry Function G1 and the pore limiting diameter was not found in the given documents. However, the documents do discuss the geometric properties of MOFs, which are inherently related to symmetry (Haldoupis et al., 2010).

Hypothesis: Symmetry Function G1 may impact the pore limiting diameter by influencing the spatial arrangement of atoms, potentially affecting the uniformity and size of the pores.

Unoccupied Energy Levels Near the Conduction Band Minimum:

Explanation: Unoccupied energy levels near the conduction band minimum can affect the electronic properties of MOFs, which in turn might influence the interaction between the framework and adsorbates. This could indirectly affect the pore limiting diameter by altering the stability and structure of the MOF.

Scientific Evidence: The documents do not explicitly link unoccupied energy levels to the pore limiting diameter. However, they discuss the impact of energy barriers and adsorption properties on MOF performance, which could be related to electronic structure (Haldoupis et al., 2010).

Hypothesis: Unoccupied energy levels near the conduction band minimum may influence the pore limiting diameter by affecting the electronic interactions within the MOF, potentially leading to structural changes that alter pore sizes.

Summary

The relationship between the identified features and the pore limiting diameter in MOFs is complex and not explicitly detailed

in the provided documents. The volume per atom is likely to influence the pore limiting diameter through its effect on atomic packing and density, potentially leading to larger or smaller pores depending on the volume. Symmetry Function G1, while not explicitly discussed, could impact the pore structure by affecting the spatial arrangement of atoms. Unoccupied energy levels near the conduction band minimum might indirectly influence the pore limiting diameter by altering the electronic properties and stability of the MOF. These hypotheses are based on the general principles discussed in the documents, such as the importance of geometric and electronic properties in determining MOF structure and function.

References

1. Chung, Y. G., Haldoupis, E., Bucior, B. J., Haranczyk, M., Lee, S., Zhang, H., Vogiatzis, K. D., Milisavljevic, M., Ling, S., Camp, J. S., Slater, B., Siepmann, J. I., Sholl, D. S., & Snurr, R. Q. (2019). Advances, Updates, and Analytics for the Computation-Ready, Experimental Metal–Organic Framework Database: CoRE MOF 2019.
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[ChatGPT Explanation]

Features Identified by ChatGPT

- Linker Length
- Metal Node Size
- Functional Groups on Linkers
- Topology of the Framework

- Flexibility of the Framework
- Presence of Defects
- Solvent Molecules in the Pores
- Coordination Geometry
- Interpenetration

Linker Length:

Explanation: The length of the organic linkers in MOFs directly affects the distance between metal nodes, thereby influencing the pore size. Longer linkers generally result in larger pore sizes, while shorter linkers lead to smaller pores.

Hypothesis: Increasing the length of the organic linkers will proportionally increase the pore limiting diameter in MOFs.

Metal Node Size:

Explanation: The size of the metal nodes can also impact the pore limiting diameter. Larger metal nodes can create more spacious frameworks, while smaller nodes may result in tighter structures.

Hypothesis: Utilizing larger metal nodes will increase the pore limiting diameter, whereas smaller metal nodes will decrease it.

Functional Groups on Linkers:

Explanation: Functional groups attached to the linkers can either obstruct or facilitate the pore space. Bulky functional groups may reduce the effective pore diameter, while smaller or more flexible groups may have less impact.

Hypothesis: The presence of bulky functional groups on linkers will decrease the pore limiting diameter, while smaller functional groups will have a minimal effect.

Topology of the Framework:

Explanation: The overall topology or arrangement of the framework can significantly influence the pore size. Certain topologies may naturally create larger or smaller pores due to the spatial arrangement of the linkers and nodes.

Hypothesis: Frameworks with more open and less dense topologies will have larger pore limiting diameters compared to more compact and dense topologies.

Flexibility of the Framework:

Explanation: The flexibility of the MOF structure can allow for dynamic changes in pore size. Flexible frameworks can adapt to external stimuli, potentially altering the pore limiting diameter.

Hypothesis: More flexible frameworks will exhibit a wider range of pore limiting diameters under different conditions compared to rigid frameworks.

Presence of Defects:

Explanation: Defects in the MOF structure, such as missing linkers or nodes, can create additional pore space or alter the existing pore structure.

Hypothesis: The presence of defects will generally increase the pore limiting diameter due to the creation of additional voids.

Solvent Molecules in the Pores:

Explanation: Solvent molecules trapped within the pores can occupy space and effectively reduce the pore limiting diameter.

Hypothesis: The presence of solvent molecules within the pores will decrease the pore limiting diameter.

Coordination Geometry:

Explanation: The coordination geometry of the metal nodes can influence the spatial arrangement of the linkers and thus the pore size. Different geometries can lead to more open or more closed structures.

Hypothesis: Metal nodes with coordination geometries that promote more open structures will increase the pore limiting diameter.

Interpenetration:

Explanation: Interpenetration occurs when multiple frameworks interlock within the same crystal lattice, effectively reducing the available pore space.

Hypothesis: The presence of interpenetration will decrease the pore limiting diameter due to the overlapping of frameworks.

Summary

The pore limiting diameter in Metal-Organic Frameworks (MOFs) is influenced by a variety of molecular features. The length of the linkers and the size of the metal nodes are primary determinants, with longer linkers and larger nodes generally increasing the pore size. Functional groups on the linkers can either obstruct or facilitate pore space, with bulky groups reducing the effective diameter. The topology of the framework and its flexibility also play crucial roles, with more open topologies and flexible structures allowing for larger or variable pore sizes. Defects within the framework can create additional voids, increasing the pore diameter, while solvent molecules trapped in the pores can reduce it. The coordination geometry of the metal nodes and the presence of interpenetration further modulate the pore size, with more open geometries and lack of interpenetration favoring larger pores. Understanding

these relationships is essential for the rational design of MOFs with desired pore characteristics.

References:

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Case study 3. Understanding toxicity of small molecules:

[XpertAT Explanation]

Features Identified by XAI Analysis

- Presence of a heteroatom bonded to three oxygen atoms
- Presence of a tertiary amine
- Presence of a carbon-oxygen single bond

Presence of a heteroatom bonded to three oxygen atoms:

Explanation: The presence of a heteroatom bonded to three oxygen atoms, such as in a phosphate group, is often associated with significant chemical reactivity due to the electronegative nature of oxygen atoms. This can influence the molecular structure and reactivity, potentially affecting the toxicity of small molecules.

Scientific Evidence: The document discusses the role of oxygen lone pairs in chemical reactivity, particularly in anomeric systems where oxygen atoms interact with strong sigma-acceptors (Alabugin et al., 2021). This suggests that the presence of multiple oxygen atoms bonded to a heteroatom can lead to increased reactivity and potentially influence toxicity.

Hypothesis: The presence of a heteroatom bonded to three oxygen atoms may increase the reactivity of a molecule, thereby influencing its toxicity profile due to potential interactions with biological targets.

Presence of a tertiary amine:

Explanation: Tertiary amines are known for their nucleophilic properties, which can lead to interactions with electrophilic sites in biological systems. This can result in various biological effects, including potential toxicity.

Scientific Evidence: The SHAP analysis indicates a positive correlation between the presence of a tertiary amine and its impact on the model, suggesting its relevance in toxicity predictions (XpertAI, 2024).

Hypothesis: Tertiary amines may contribute to the toxicity of small molecules through their nucleophilic interactions with biological macromolecules, potentially leading to adverse effects.

Presence of a carbon-oxygen single bond:

Explanation: Carbon-oxygen single bonds are common in various functional groups such as alcohols and ethers. These bonds can influence the solubility, reactivity, and overall chemical behavior of a molecule, which in turn can affect its toxicity.

Scientific Evidence: The SHAP analysis shows a positive correlation between the presence of a carbon-oxygen single bond and its impact on the model, indicating its significance in toxicity predictions (XpertAI, 2024).

Hypothesis: The presence of carbon-oxygen single bonds may affect the toxicity of small molecules by altering their chemical properties, such as solubility and reactivity, which can influence their interaction with biological systems.

Summary

The analysis of features identified by XAI in relation to the toxicity of small molecules reveals several key insights. The presence of a heteroatom bonded to three oxygen atoms, such as in phosphate groups, is associated with increased chemical reactivity due to the electronegative nature of oxygen atoms, potentially influencing toxicity (Alabugin et al., 2021). Tertiary amines, known for their nucleophilic properties, may interact with electrophilic sites in biological systems, contributing to toxicity (XpertAI, 2023). Additionally, carbon-oxygen single bonds, prevalent in functional groups like alcohols and ethers, can affect the solubility and reactivity of molecules, thereby impacting their toxicity (XpertAI, 2023). These features highlight the complex interplay between chemical structure and biological activity, underscoring the importance of understanding molecular interactions in toxicity predictions.

References

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[ChatGPT Explanation]

Features Identified by ChatGPT

- Molecular weight
- Lipophilicity (LogP)
- Hydrogen bond donors
- Hydrogen bond acceptors
- Polar surface area (PSA)
- Aromatic rings
- Functional groups (e.g., amines, carboxylic acids, halogens)
- Electrophilicity
- Metabolic stability
- Reactive functional groups (e.g., epoxides, aldehydes)
- Structural alerts (e.g., nitro groups, anilines)
- pKa
- Stereochemistry

Molecular weight:

Explanation: Higher molecular weight can influence the distribution, metabolism, and excretion of small molecules. Generally, molecules with very high molecular weights may have reduced permeability and bioavailability, potentially leading to accumulation and toxicity.

Hypothesis: Molecules with molecular weights above a certain threshold (e.g., 500 Da) are more likely to exhibit toxicity due to poor excretion and potential accumulation in tissues.

Lipophilicity (LogP):

Explanation: Lipophilicity, often measured as LogP, affects the ability of a molecule to cross cell membranes. Highly lipophilic molecules can accumulate in lipid-rich tissues, potentially leading to toxicity. Conversely, very hydrophilic molecules may have poor cell membrane permeability.

Hypothesis: Molecules with a LogP value outside the optimal range (typically between 1 and 3) are more likely to be toxic due to either excessive accumulation in lipid tissues or poor cellular uptake.

Hydrogen bond donors:

Explanation: Hydrogen bond donors can influence the solubility and permeability of molecules. Excessive hydrogen bonding can reduce membrane permeability, affecting distribution and excretion.

Hypothesis: Molecules with a high number of hydrogen bond donors are more likely to exhibit toxicity due to poor permeability and potential accumulation.

Hydrogen bond acceptors:

Explanation: Similar to hydrogen bond donors, hydrogen bond acceptors can affect solubility and permeability. A high number of hydrogen bond acceptors can lead to poor membrane permeability.

Hypothesis: Molecules with a high number of hydrogen bond acceptors are more likely to be toxic due to reduced permeability and potential bioaccumulation.

Polar surface area (PSA):

Explanation: PSA is a measure of the surface area occupied by polar atoms. High PSA can reduce membrane permeability and affect the distribution of the molecule.

Hypothesis: Molecules with high PSA are more likely to exhibit toxicity due to poor permeability and potential accumulation in non-target tissues.

Aromatic rings:

Explanation: Aromatic rings can contribute to the stability and reactivity of molecules. However, they can also lead to the formation of reactive metabolites, which can be toxic.

Hypothesis: Molecules with multiple aromatic rings are more likely to be toxic due to the potential formation of reactive metabolites.

Functional groups (e.g., amines, carboxylic acids, halogens):

Explanation: Different functional groups can influence the reactivity, solubility, and metabolism of molecules. For example, halogens can increase lipophilicity, while amines and carboxylic acids can affect solubility and ionization.

Hypothesis: Molecules with certain functional groups (e.g., halogens, nitro groups) are more likely to be toxic due to increased reactivity and potential for forming reactive intermediates.

Electrophilicity:

Explanation: Electrophilic molecules can react with nucleophilic sites in biological macromolecules, leading to toxicity. This can result in covalent binding to proteins, DNA, and other cellular components.

Hypothesis: Highly electrophilic molecules are more likely to be toxic due to their potential to form covalent bonds with biological macromolecules.

Metabolic stability:

Explanation: Metabolic stability affects the duration and intensity of a molecule's action. Molecules that are rapidly metabolized may produce toxic metabolites, while those that are highly stable may accumulate and cause toxicity.

Hypothesis: Molecules with either very high or very low metabolic stability are more likely to be toxic due to the formation of toxic metabolites or accumulation, respectively.

Reactive functional groups (e.g., epoxides, aldehydes):

Explanation: Reactive functional groups can form covalent bonds with biological macromolecules, leading to toxicity. These groups can also generate reactive oxygen species (ROS), causing oxidative stress.

Hypothesis: Molecules with reactive functional groups are more likely to be toxic due to their potential to form covalent bonds and generate ROS.

Structural alerts (e.g., nitro groups, anilines):

Explanation: Structural alerts are specific substructures known to be associated with toxicity. For example, nitro groups and anilines can undergo metabolic activation to form reactive intermediates.

Hypothesis: Molecules containing structural alerts are more likely to be toxic due to the formation of reactive intermediates during metabolism.

pKa:

Explanation: The pKa of a molecule affects its ionization state at physiological pH, influencing solubility, permeability, and distribution. Molecules with extreme pKa values may have poor permeability and bioavailability.

Hypothesis: Molecules with pKa values far from physiological pH (7.4) are more likely to be toxic due to poor permeability and potential accumulation.

Stereochemistry:

Explanation: Stereochemistry can influence the binding of molecules to biological targets and their metabolism. Enantiomers can have different pharmacokinetic and toxicological profiles.

Hypothesis: Molecules with chiral centers are more likely to exhibit stereochemistry-dependent toxicity due to differences in binding affinity and metabolic pathways.

Summary

The toxicity of small molecules is influenced by a variety of molecular features, including molecular weight, lipophilicity, hydrogen bond donors and acceptors, polar surface area, aromatic rings, functional groups, electrophilicity, metabolic stability, reactive functional groups, structural alerts, pKa, and stereochemistry. Each of these features can affect the solubility, permeability, distribution, metabolism, and reactivity of the molecules, ultimately influencing their potential to cause toxicity. Understanding these relationships can help in the design of safer and more effective small molecules.

References

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Case study 4. Understanding solubility of small molecules:

[XpertAT Explanation]

Features Identified by XAI Analysis

- Presence of an atom at an aromatic/non-aromatic boundary
- Presence of two heteroatoms bonded to each other
- Presence of an atom with three heteroatom neighbors

Presence of an atom at an aromatic/non-aromatic boundary:

Explanation: This feature is negatively correlated with solubility, as indicated by its strong negative correlation with SHAP values. The presence of such boundaries may affect the molecular planarity and symmetry, which are known to influence solubility.

Scientific Evidence: The SHAP analysis shows a strong negative correlation (correlation coefficient: -0.9531) with an average impact of 0.4801 (XpertAI, 2024). Additionally, disrupting molecular planarity and symmetry by eliminating aromaticity can enhance solubility (Ishikawa & Hashimoto, 2011).

Hypothesis: The presence of an atom at an aromatic/non-aromatic boundary reduces solubility by maintaining molecular planarity and symmetry, which are less favorable for solubility.

Presence of two heteroatoms bonded to each other:

Explanation: This feature also shows a strong negative correlation with solubility. The bonding of heteroatoms can influence the electronic distribution and hydrogen bonding potential, which are critical for solubility.

Scientific Evidence: The SHAP analysis indicates a strong negative correlation (correlation coefficient: -0.9688) with an average impact of 0.3475 (XpertAI, 2024). The presence of polar atoms like nitrogen or oxygen can alter solubility by affecting hydrogen bonding (Walker, 2017).

Hypothesis: The bonding of two heteroatoms may reduce solubility by altering the electronic distribution and reducing favorable hydrogen bonding interactions.

Presence of an atom with three heteroatom neighbors:

Explanation: This feature is negatively correlated with solubility, likely due to the complex electronic environment

created by multiple heteroatom neighbors, which can affect solubility.

Scientific Evidence: The SHAP analysis shows a strong negative correlation (correlation coefficient: -0.9601) with an average impact of 0.2489 (XpertAI, 2024). The presence of multiple heteroatoms can influence solubility by affecting the molecule's electronic properties (Walker, 2017).

Hypothesis: An atom with three heteroatom neighbors may reduce solubility by creating an electronic environment that is less conducive to solubility.

Summary

The features identified by the XAI analysis, such as the presence of an atom at an aromatic/non-aromatic boundary, two heteroatoms bonded to each other, and an atom with three heteroatom neighbors, all show strong negative correlations with solubility. These features likely influence solubility by affecting molecular planarity, symmetry, electronic distribution, and hydrogen bonding potential. The presence of aromatic boundaries and heteroatom interactions can maintain molecular structures that are less favorable for solubility, as supported by the SHAP analysis and literature on molecular modifications for solubility enhancement (XpertAI, 2023; Ishikawa & Hashimoto, 2011; Walker, 2017).

References

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[ChatGPT Explanation]

Features Identified by ChatGPT

- Polarity
- Hydrogen Bonding
- Molecular Size
- Functional Groups
- Ionizability
- Aromaticity
- Branching
- Presence of Halogens

Polarity:

Explanation: Polarity refers to the distribution of electric charge around a molecule. Polar molecules have regions with partial positive and negative charges, which can interact favorably with water molecules, a polar solvent. This interaction enhances solubility.

Hypothesis: Molecules with higher polarity will exhibit greater solubility in polar solvents like water due to stronger dipole-dipole interactions.

Hydrogen Bonding:

Explanation: Hydrogen bonding occurs when a hydrogen atom covalently bonded to a highly electronegative atom (like oxygen or nitrogen) interacts with another electronegative atom. Molecules capable of hydrogen bonding can form strong interactions with water molecules, increasing solubility.

Hypothesis: Molecules that can form hydrogen bonds will have

higher solubility in water due to the formation of strong intermolecular hydrogen bonds with water molecules.

Molecular Size:

Explanation: Larger molecules have more extensive surface areas, which can lead to increased van der Waals interactions. However, larger molecules also have more complex structures that may not interact as favorably with solvent molecules, potentially decreasing solubility.

Hypothesis: Smaller molecules will generally be more soluble in water than larger molecules due to less steric hindrance and more efficient interaction with solvent molecules.

Functional Groups:

Explanation: Functional groups such as hydroxyl (-OH), carboxyl (-COOH), and amino (-NH₂) groups can significantly affect solubility. These groups can form hydrogen bonds and interact with polar solvents, enhancing solubility.

Hypothesis: Molecules with polar functional groups will have higher solubility in polar solvents due to their ability to form hydrogen bonds and other polar interactions.

Ionizability:

Explanation: Ionizable groups can dissociate in water to form ions, which are highly soluble due to their strong interactions with water molecules. This is particularly true for acids and bases.

Hypothesis: Molecules that can ionize in water will have higher solubility due to the formation of highly soluble ions.

Aromaticity:

Explanation: Aromatic compounds have delocalized π -electrons, which can affect their solubility. While aromaticity can enhance solubility in non-polar solvents, it may reduce solubility in polar solvents due to the lack of polar interactions.

Hypothesis: Aromatic molecules will have lower solubility in polar solvents like water compared to non-aromatic molecules of similar size and functionalization.

Branching:

Explanation: Branching in molecules can reduce the surface area available for intermolecular interactions, potentially increasing solubility in polar solvents by reducing van der Waals interactions.

Hypothesis: Branched molecules will have higher solubility in polar solvents compared to their linear counterparts due to reduced van der Waals interactions.

Presence of Halogens:

Explanation: Halogens are electronegative and can affect the polarity of molecules. However, they also increase molecular size and can form strong van der Waals interactions, which may reduce solubility in polar solvents.

Hypothesis: The presence of halogens will generally decrease solubility in polar solvents due to increased molecular size and stronger van der Waals interactions.

Summary

The solubility of small molecules is influenced by a variety of molecular features. Polarity and hydrogen bonding are critical factors that enhance solubility in polar solvents like water. Smaller molecules and those with polar functional groups also tend to be more soluble due to more efficient interactions with

solvent molecules. Ionizable groups significantly increase solubility by forming highly soluble ions. Aromaticity generally reduces solubility in polar solvents, while branching can increase it by reducing van der Waals interactions. The presence of halogens typically decreases solubility in polar solvents due to increased molecular size and stronger van der Waals interactions. Understanding these relationships allows for the prediction and manipulation of solubility in various solvents, which is crucial in fields such as pharmaceuticals and materials science.

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Case study 5. Understanding upper flammability limit of organic molecules:

[XpertAT Explanation]

Features Identified by XAI Analysis

- Structural Information Content Index (Neighborhood Symmetry of Zero-Order)

- Information Content Index (Neighborhood Symmetry of Order)
- Dipole Moment

Relationship of Each Feature with the Upper Flammability Limit of Organic Molecules

Structural Information Content Index (Neighborhood Symmetry of Zero-Order)

Explanation: This feature quantifies the symmetry of a molecule's neighborhood at the zero-order level, which can influence how the molecule interacts with its environment, including its flammability characteristics.

Scientific Evidence: The document by Gharagheizi (2009) discusses the use of information index descriptors like SIC0, which account for neighborhood symmetry, in predicting the upper flammability limit (UFL) of organic compounds. An increase in SIC0 correlates with an increase in UFL (Gharagheizi, 2009).

Hypothesis: The Structural Information Content Index (Neighborhood Symmetry of Zero-Order) likely affects the UFL by influencing the molecular stability and reactivity, which are critical factors in determining flammability.

Information Content Index (Neighborhood Symmetry of Order)

Explanation: This feature is a generalized form of the previous index, focusing on the symmetry of molecular neighborhoods at various orders. It provides a broader perspective on molecular symmetry and its impact on flammability.

Scientific Evidence: The same study by Gharagheizi (2009) can be referenced here, as it discusses the role of information content indices in predicting UFL. The broader term "Information Content Index (Neighborhood Symmetry of Order)" would encompass various

levels of symmetry, potentially offering a more comprehensive understanding of molecular interactions affecting UFL.

Hypothesis: The Information Content Index (Neighborhood Symmetry of Order) impacts the UFL by providing a detailed account of molecular symmetry, which influences how molecules interact with oxygen and other reactants during combustion.

Dipole Moment

Explanation: The dipole moment measures the separation of positive and negative charges within a molecule, affecting its polarity and interactions with other molecules, including those involved in combustion.

Scientific Evidence: While the provided documents do not explicitly discuss the dipole moment's impact on UFL, it is well-known in the literature that dipole moments can influence molecular interactions and stability, which are critical for flammability (Yuan et al., 2019).

Hypothesis: The dipole moment affects the UFL by altering the molecule's polarity, which can influence its reactivity and the energy required for combustion.

Summary

The features identified by the XAI analysis, including the Structural Information Content Index (Neighborhood Symmetry of Zero-Order), Information Content Index (Neighborhood Symmetry of Order), and Dipole Moment, all play significant roles in determining the upper flammability limit (UFL) of organic molecules. The Structural Information Content Index (Neighborhood Symmetry of Zero-Order) and its generalized form, Information Content Index (Neighborhood Symmetry of Order), quantify molecular symmetry, which influences molecular stability and reactivity. These factors can be crucial in

determining how easily a molecule can ignite and sustain combustion. The dipole moment, although not explicitly discussed in the provided documents, could affect molecular interactions and stability, thereby influencing flammability. These features collectively provide a comprehensive understanding of the molecular characteristics that impact the UFL of organic compounds.

References

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[ChatGPT Explanation]

Features Identified by ChatGPT

- Molecular Size
- Molecular Shape
- Functional Groups
- Degree of Unsaturation
- Presence of Halogens
- Oxygen Content
- Hydrogen-to-Carbon Ratio
- Molecular Polarity
- Aromaticity

Molecular Size:

Explanation: Larger molecules generally have higher boiling points and lower vapor pressures, which can affect their flammability limits. The upper flammability limit (UFL) tends to decrease with increasing molecular size because larger molecules are less volatile and produce fewer flammable vapors.

Hypothesis: As the molecular size increases, the upper flammability limit of organic molecules decreases due to reduced volatility and vapor production.

Molecular Shape:

Explanation: The shape of a molecule can influence its ability to mix with air and form a flammable mixture. Branched molecules often have lower UFLs compared to their straight-chain counterparts because they are more volatile and can more easily form flammable mixtures.

Hypothesis: Branched organic molecules have a lower upper flammability limit compared to straight-chain molecules due to their higher volatility and ease of mixing with air.

Functional Groups:

Explanation: Functional groups such as hydroxyl (-OH), carbonyl (C=O), and amino (-NH₂) groups can significantly affect the flammability of organic molecules. For instance, alcohols generally have higher UFLs compared to hydrocarbons due to the presence of the hydroxyl group, which can form hydrogen bonds and reduce volatility.

Hypothesis: The presence of polar functional groups increases the upper flammability limit of organic molecules by reducing their volatility.

Degree of Unsaturation:

Explanation: Unsaturated molecules (those with double or triple bonds) tend to have higher UFLs compared to their saturated counterparts. This is because unsaturated bonds can participate in additional reactions that stabilize the molecule, making it less likely to form flammable vapors.

Hypothesis: Increased degree of unsaturation in organic molecules leads to a higher upper flammability limit due to the stabilization provided by double and triple bonds.

Presence of Halogens:

Explanation: Halogenated organic compounds generally have higher UFLs because halogens (like chlorine, fluorine) increase the molecular weight and reduce volatility. Additionally, halogens can act as flame retardants by interfering with the combustion process.

Hypothesis: The presence of halogens in organic molecules increases the upper flammability limit by reducing volatility and acting as flame retardants.

Oxygen Content:

Explanation: Molecules with higher oxygen content, such as ethers and esters, tend to have higher UFLs. Oxygen atoms can form hydrogen bonds and increase the overall polarity of the molecule, reducing its volatility.

Hypothesis: Higher oxygen content in organic molecules increases the upper flammability limit by enhancing molecular polarity and reducing volatility.

Hydrogen-to-Carbon Ratio:

Explanation: A higher hydrogen-to-carbon ratio generally means a molecule is more saturated and less polar, which can lower the UFL. Saturated hydrocarbons are more volatile and can more

easily form flammable mixtures.

Hypothesis: A higher hydrogen-to-carbon ratio in organic molecules decreases the upper flammability limit due to increased volatility.

Molecular Polarity:

Explanation: Polar molecules tend to have higher UFLs because they are less volatile and more likely to form hydrogen bonds, which stabilize the liquid phase and reduce the formation of flammable vapors.

Hypothesis: Increased molecular polarity in organic molecules leads to a higher upper flammability limit by reducing volatility and enhancing liquid-phase stability.

Aromaticity:

Explanation: Aromatic compounds, such as benzene, generally have higher UFLs compared to aliphatic compounds. The delocalized π -electrons in aromatic rings provide additional stability, making these molecules less volatile.

Hypothesis: Aromaticity in organic molecules increases the upper flammability limit due to the stabilizing effect of delocalized π -electrons, which reduces volatility.

Summary

The upper flammability limit (UFL) of organic molecules is influenced by a variety of molecular features. Larger molecules and those with branched structures tend to have lower UFLs due to increased volatility. Functional groups, particularly polar ones, generally increase the UFL by reducing volatility. Unsaturated molecules and those containing halogens or higher oxygen content also exhibit higher UFLs due to stabilization effects and reduced volatility. The hydrogen-to-carbon ratio

inversely affects the UFL, with higher ratios leading to lower UFLs. Molecular polarity and aromaticity both contribute to higher UFLs by stabilizing the liquid phase and reducing the formation of flammable vapors. These relationships highlight the complex interplay between molecular structure and flammability, providing a basis for predicting and controlling the flammability of organic compounds.

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