

SNS COLLEGE OF PHARMACY AND HEALTH SCIENCES

Affiliated To The Tamil Nadu Dr. MGR Medical University, Chennai

Approved by Pharmacy Council of India, New Delhi.

Coimbatore -641035



COURSE NAME : COMPUTER AIDED DRUG DESIGN(BP 807 ET)

VIII SEM / IV YEAR

TOPIC :TAFTS STERIC CONSTANT

INTRODUCTION TO TAFT'S STERIC CONSTANT

What is Taft's Steric Constant?

Taft's Steric Constant (E_s) is a parameter that measures the **steric hindrance** of a substituent in a molecule.

$$\begin{array}{c} \text{R} \\ | \\ \text{C} - \text{O} - \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$$

LARGE SUBSTITUENT = HIGH E_s

$$\begin{array}{c} \text{R} \\ | \\ \text{C} - \text{O} - \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$$

SMALL SUBSTITUENT = LOW E_s

MEASURES BULK AND SIZE OF GROUPS



Large Group Small Group

PREDICTS MOLECULAR FITTING



Optimal Fit

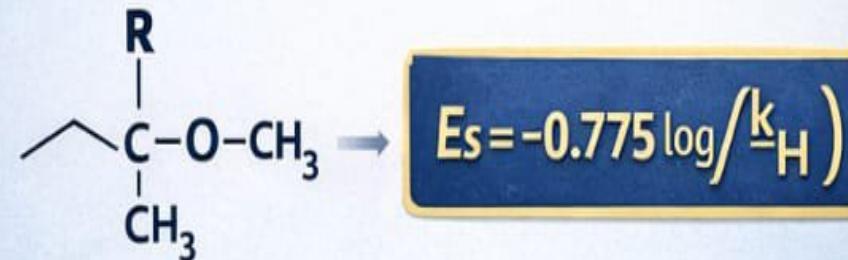
AIDS IN DRUG DESIGN

- Helps Optimize Drug Binding
- Improves Bioavailability

TAFT'S STERIC CONSTANT

Definition

Taft's Steric Constant (E_s) measures the **steric hindrance** introduced by a substituent (R) in a molecule.



- k_x = Reaction rate with substituent X
- k_H = Reaction rate with hydrogen

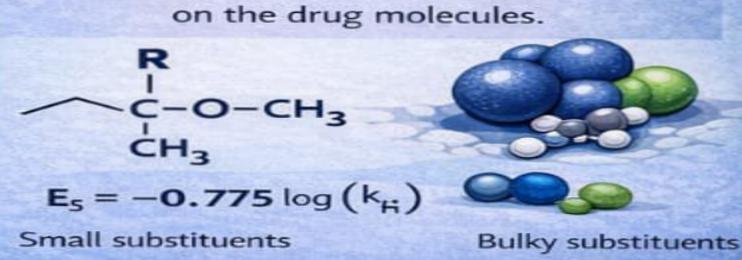
THEORY BEHIND TAFT'S STERIC CONSTANT

Taft's Steric Constant (E_s) helps in optimizing the **shape and fit** of drug candidates by considering **steric hindrance** of (R).

Molecular Modeling
Computer models simulate how drug molecules fit into target protein binding sites.



Steric Hindrance Analysis
Taft's Steric Constant (E_s) is used to analyze the size and bulkiness of substituents on the drug molecules.


$$E_s = -0.775 \log \left(\frac{k_H}{k_X} \right)$$

Optimization
Aids in optimizing substituents to improve binding affinity and pharmacokinetic properties.



- ✓ Better Binding
- ✓ Improved Drug Properties

Role in QSAR / CADD (Mathematical form)

$$E_s = -0.775 \log \left(\frac{k_H}{k_X} \right)$$

E_s quantifies the steric hindrance; higher E_s means bulkier groups; lower E_s means smaller groups



TAFT'S STERIC EQUATION

Taft's Steric Constant Equation

$$E_s = -0.775 \log \left(\frac{k_x}{k_H} \right)$$

Where:

- E_s = Taft's steric constant (steric parameter)
- k_x = Rate constant of reaction with substituent X
- k_H = Rate constant of reaction with hydrogen (reference substituent)
- -0.775 = Empirical constant derived from experimental calibration

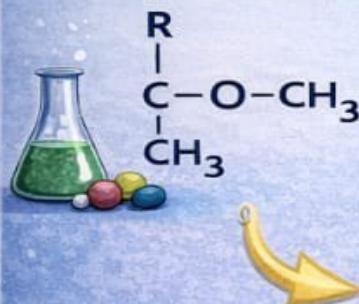
TYPES OF TAFTS STERIC CONSTANT

Taft's Steric Constant (E_s) helps in optimizing the **shape and fit** of drug candidates by considering **steric hindrance** of (R).

Original E_s

$$E_s = 0.775 \log \left(\frac{K_s}{K_n} \right)$$

- Introduced by Taft in 1956
- Measures steric hindrance relative to hydrogen (reference)

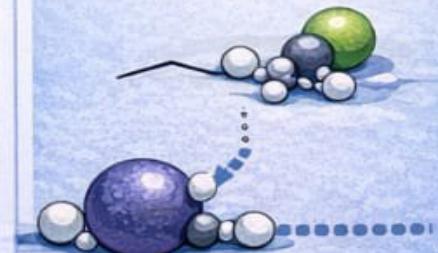


E_s^{\max}

$$E_s^{\max} = -1.24 \log \left(\frac{K_s}{K_n} \right)$$

- Derived by Topsom in the late 1960s
- Measures steric hindrance with a larger empirical constant

$$E_s^{\max} = -1.24 \text{ to } -1.35$$

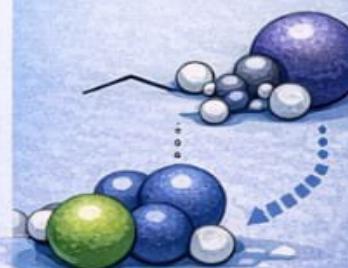


E_s^{old}

$$E_s^{\text{old}} = -1.0 \log \left(\frac{K_s}{K_n} \right)$$

- An earlier variant of Taft's steric constant
- Uses -1.0 instead of -0.775 as the empirical constant

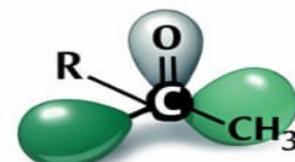
$$E_s^{\text{old}} = -1.0$$



COMPARISON

Taft Steric vs. Hammett Constant

Taft Steric Parameter (E_s)



Steric Effects



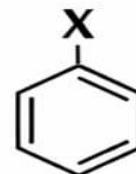
Small Group
(Low E_s)



Large Group
(High E_s)



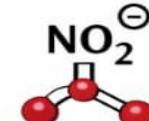
Hammett Constant (σ)



Electronic Effects



Electron-Donating
(Negative σ)

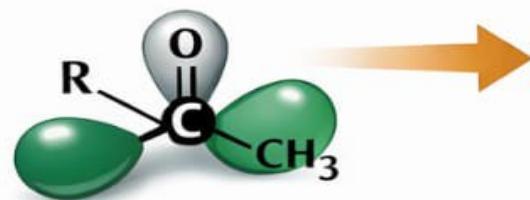


Electron-Withdrawing
(Positive σ)



ROLE OF TAFTS STERIC CONSTANT IN QSAR

Taft Steric Parameter (E_s)



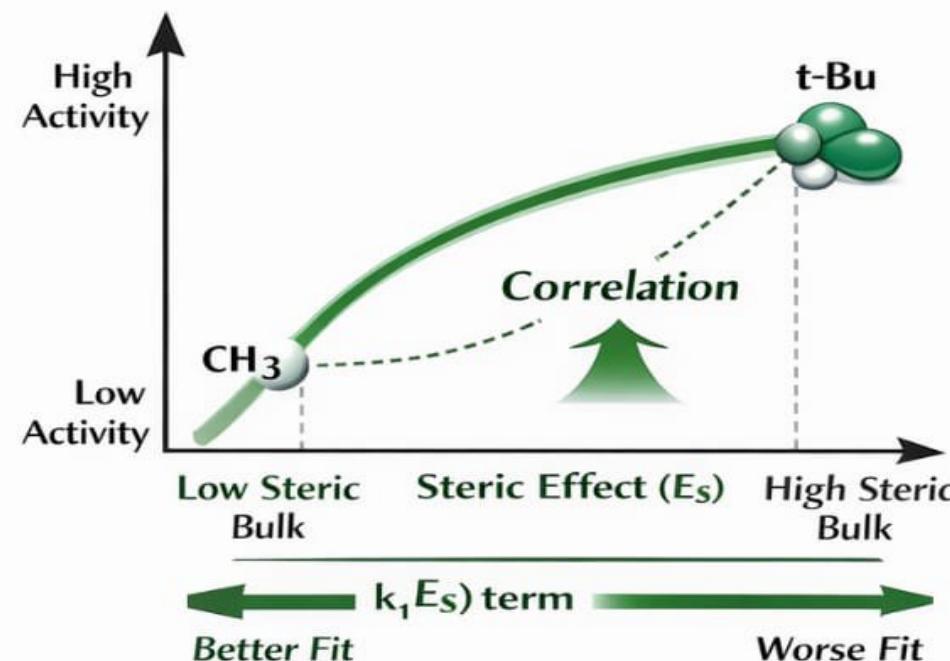
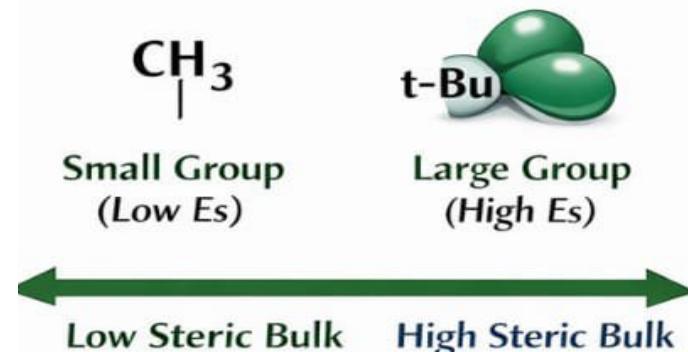
In QSAR Studies:

QSAR Equation: Activity = $k(E_s) + k_2 + k_3\sigma + \dots$

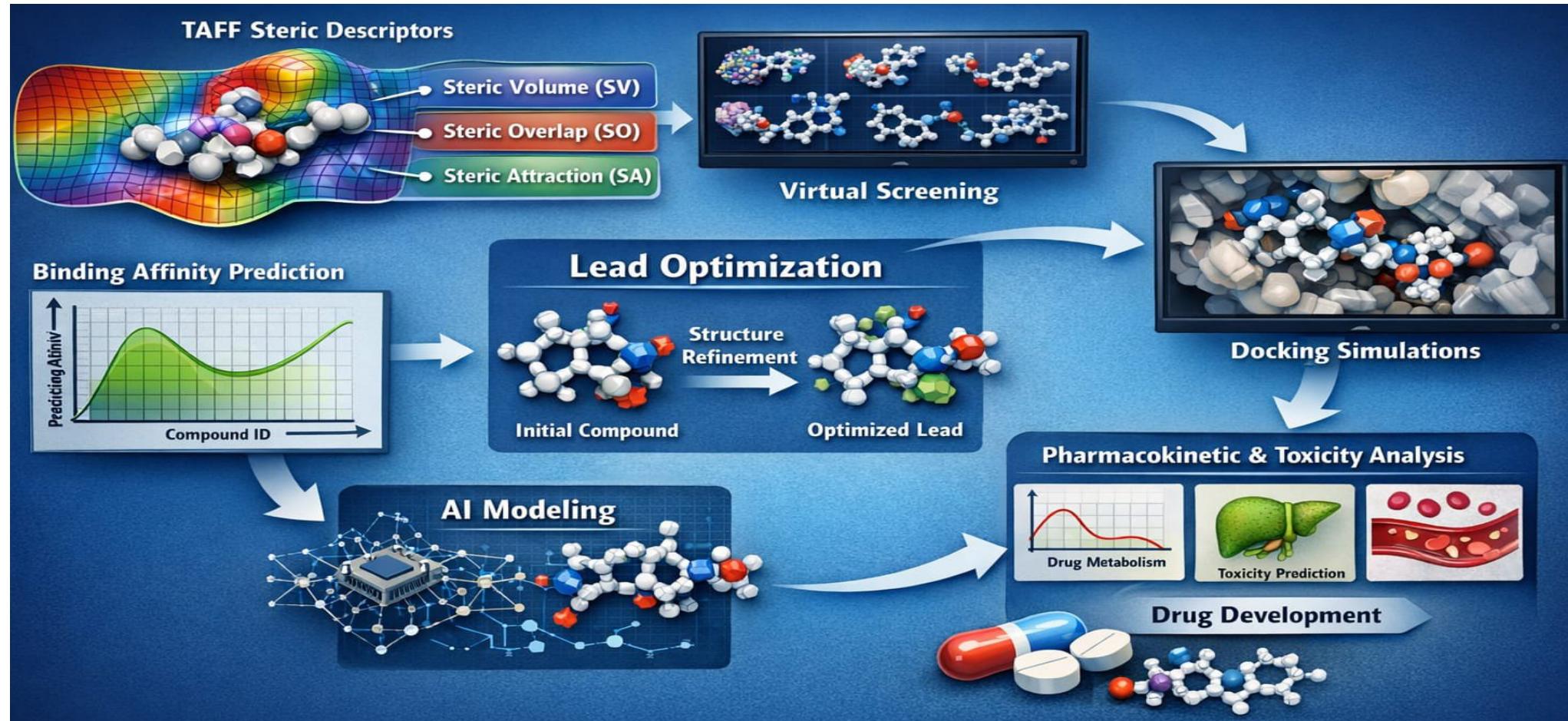
E_s term incorporated into QSAR equations to study steric effects on biological activity

Taft Steric Parameter (E_s)

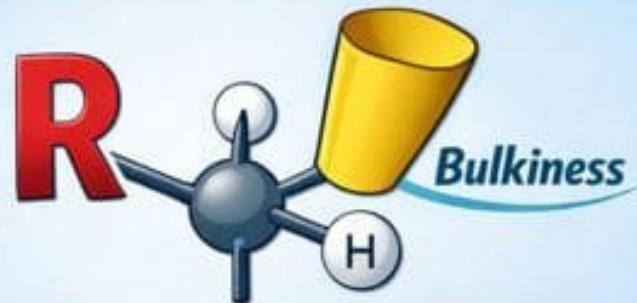
Measures Steric Effects of Substituents



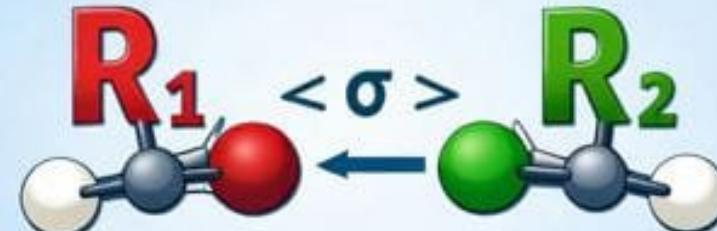
APPLICATIONS OF TAFTS STERIC CONSTANT IN CADD



ADVANTAGES



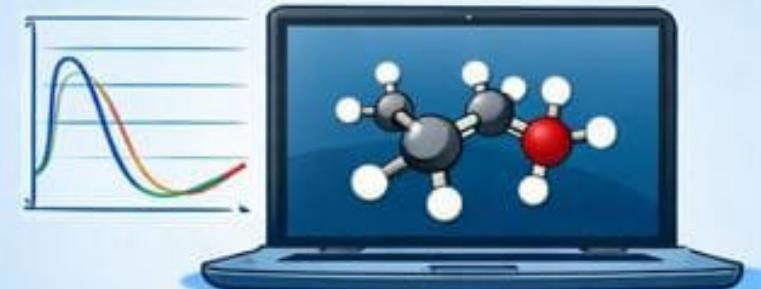
Measures Steric Effects



Comparing Substituents



Helps in Reaction Analysis

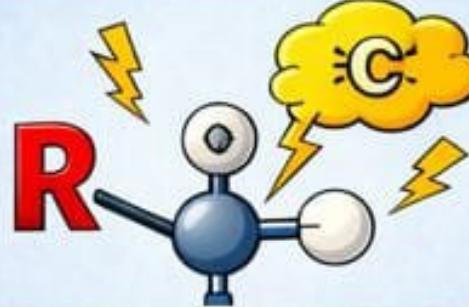


Aids in Molecular Modeling

DISADVANTAGES



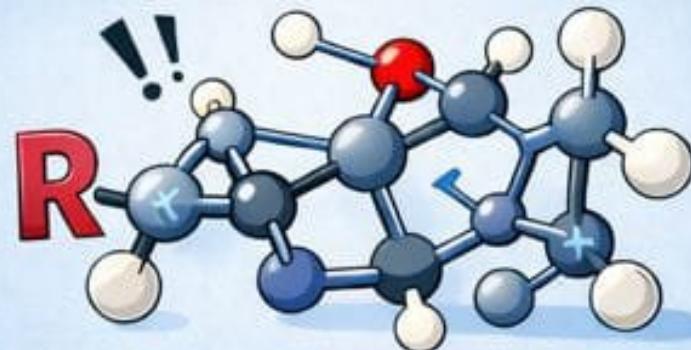
Limited Scope



Doesn't Consider Electron Effects

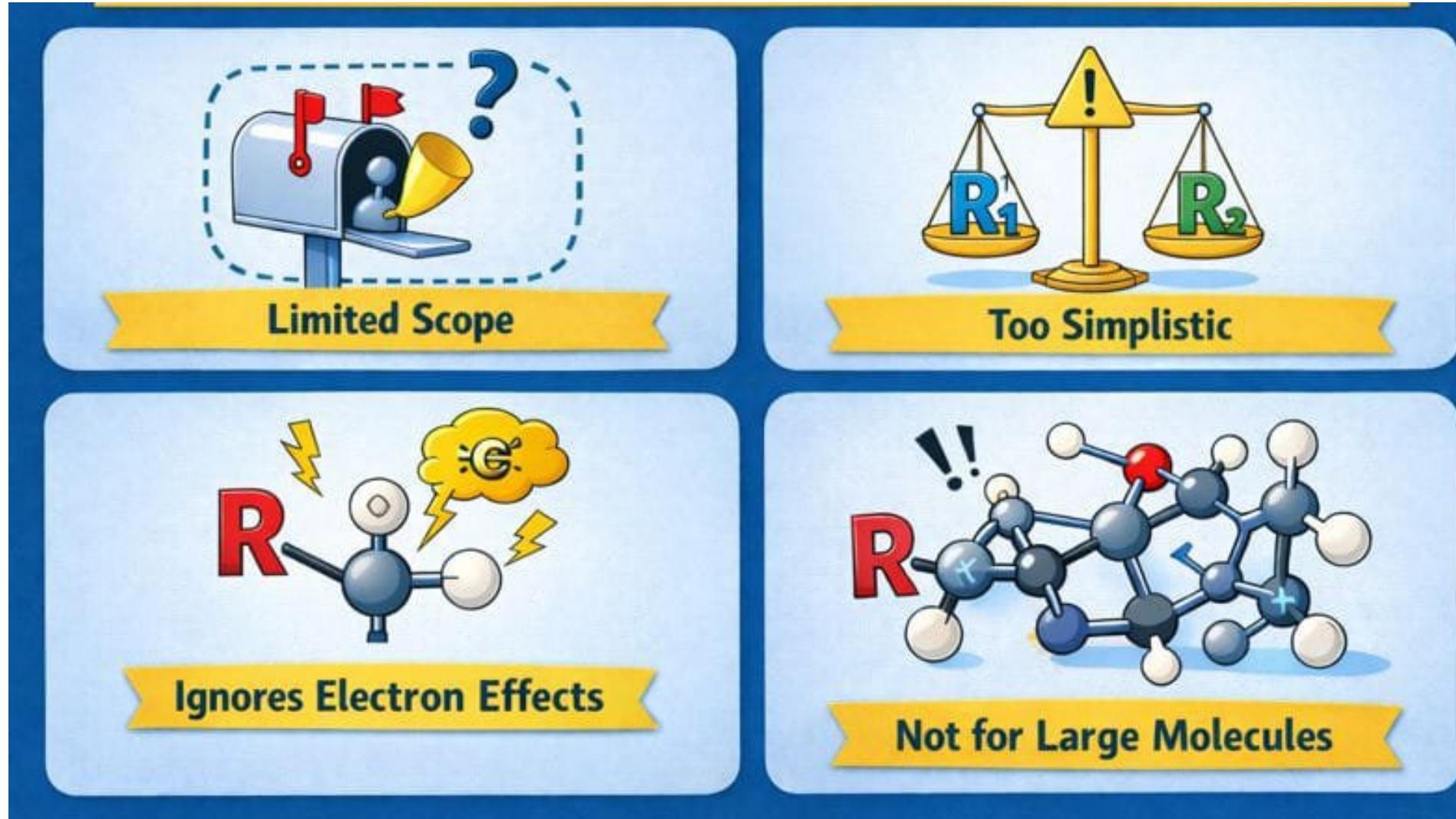


Relative Value



Difficult for Large Molecules

LIMITATIONS OF TAFTS STERIC CONSTANT

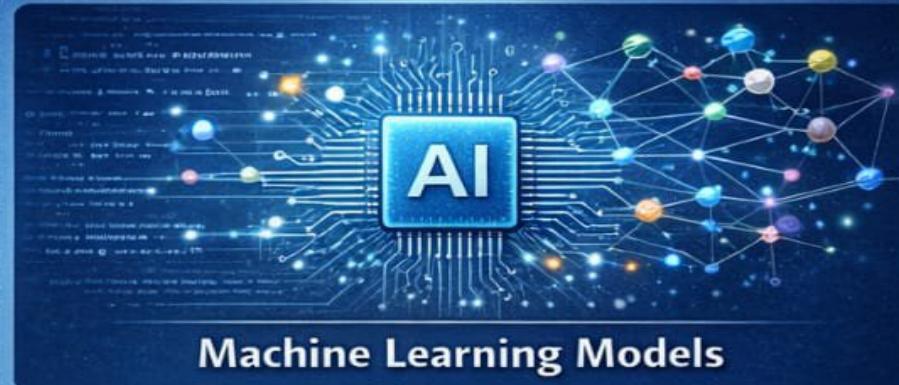


MODERN ALTERNATIVES AND EXTENSIONS

Force Field Refinements



Machine Learning Models



Quantum Mechanics-based Methods



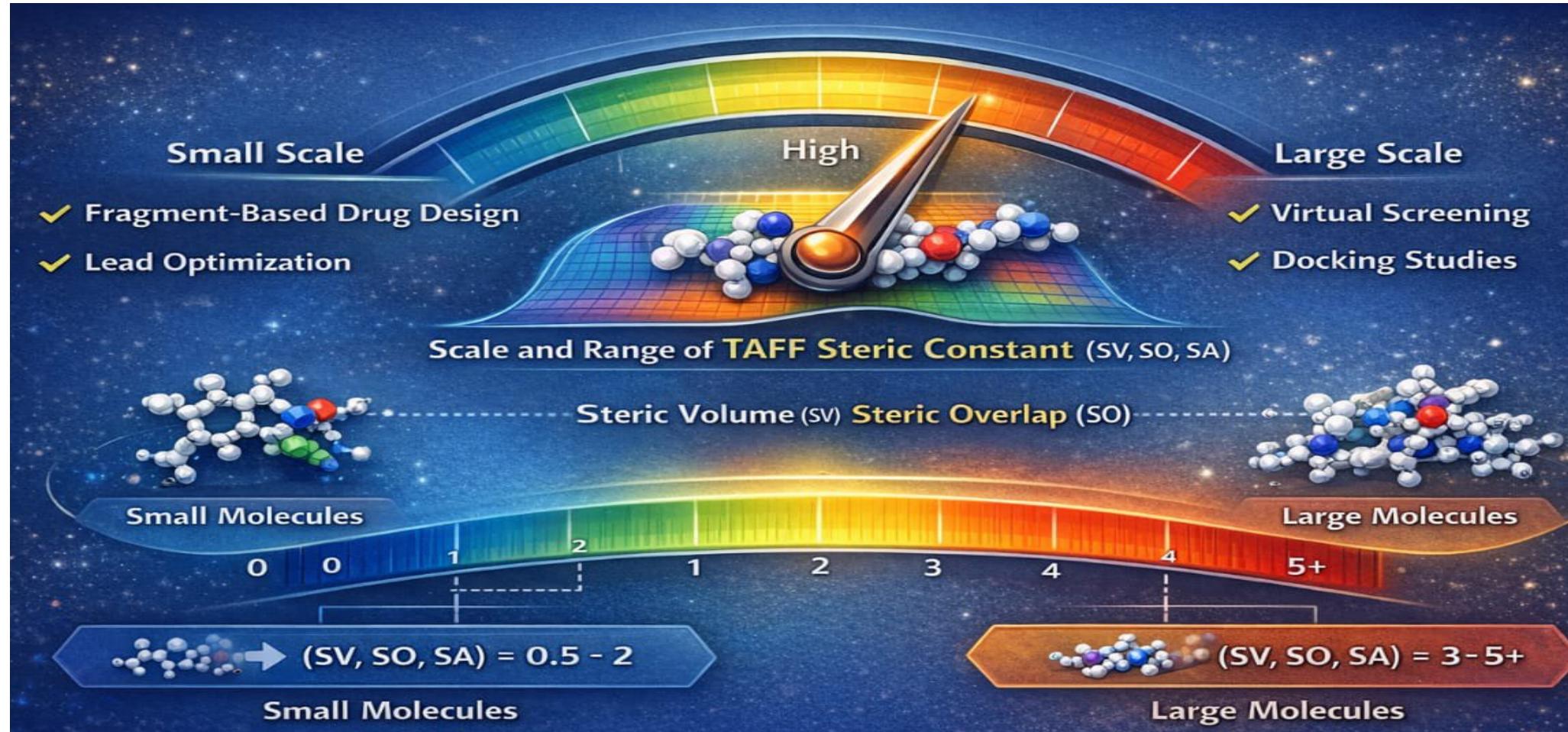
Hybrid Computational Approaches



ROLE OF TAFTS STERIC CONSTANT



SCALE AND RANGE OF TAFTS STERIC CONSTANT



ASSESSMENTS

- 1).** What is Taft's steric constant (E_s)?

- 2).** What does E_s represent in QSAR?

- 3).** Which effect is measured by Taft's steric constant

- 4).** What is the E_s value of hydrogen ($-H$)?

- 5)** More negative E_s value indicates what?



6). In CADD, Taft's steric constant helps to predict which interaction?

7). Which type of QSAR uses Taft's steric constant?

8). Name one bulky substituent with a highly negative σ value.

9). Does Taft's steric constant increase or decrease with steric bulk?

10). Write the symbol used for Taft's steric constant.



SUMMARY

Definition

Quantifies the steric effects of molecules using three key descriptors:

- ✓ Steric Volume (SV)
- ✓ Steric Overlap (SO)
- ✓ Steric Attraction (SA)

Role in Drug Design

- ✓ Virtual Screening
- ✓ Docking Simulations
- ✓ Lead Optimization

Advantages

- ✓ Efficient for Steric Analysis
- ✓ Facilitates High-Throughput Screening
- ✓ Helps in Lead Optimization

$(SV, SO, SA) = 0.5 - 2$

Small Molecules

TAFF Steric Constant is a computational approach used in computer-aided drug design to evaluate steric properties of molecules using descriptors such as Steric Volume, Steric Overlap, and Steric Attraction.

Limitations

- ✗ Oversimplifies Molecular Interactions
- ✗ Ignores Electrostatic Effects
- ✗ Can Be Computationally Demanding

$(SV, SO, SA) = 3 - 5+$

Large Molecules

06-11-2025

CADD | Mr. S. SRI VIKRAM | AP | SNSCPHS

18/20

REFERENCE

- 1)** Aman Thakur, Vineet Mehta, Priyanka Nagu & Kiran Goutam - Computer-Aided Drug Design
- 2)** Hansch, C., Leo, A. & Hoekman, D. Exploring QSAR: Hydrophobic, Electronic, and Steric Constants
- 3)** Yvonne C. Martin Quantitative Drug Design: A Critical Introduction

