

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)

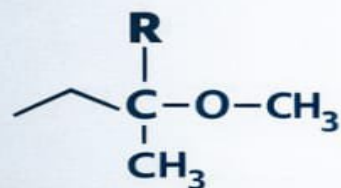
VIII SEM / IV YEAR

TOPIC :TAFTS STERIC CONSTANT

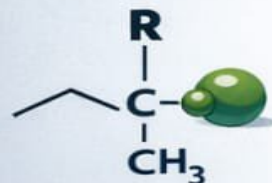
INTRODUCTION TO TAFT'S STERIC CONSTANT

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.



LARGE SUBSTITUENT = HIGH E_s



SMALL SUBSTITUENT = LOW E_s

MEASURES BULK AND SIZE OF GROUPS



Large Group



Small Group

PREDICTS MOLECULAR FITTING



AIDS IN DRUG DESIGN

- Helps Optimize Drug Binding

- Improves Bioavailability

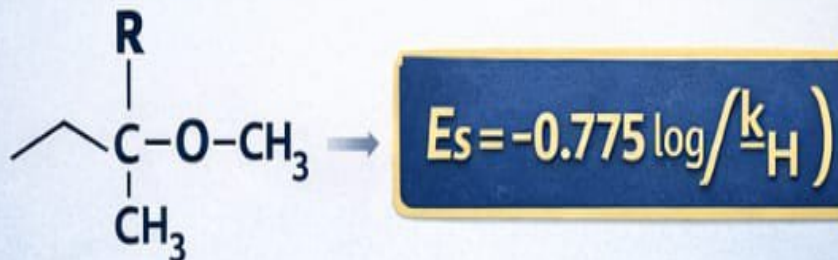


TAFT'S STERIC CONSTANT

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.


CC(R)OC

$E_s = -0.775 \log(k_H)$

Small substituents Bulky substituents

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


- ✓ Better Binding
- ✓ Improved Drug Properties



Role in QSAR / CADD (Mathematical form)

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

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

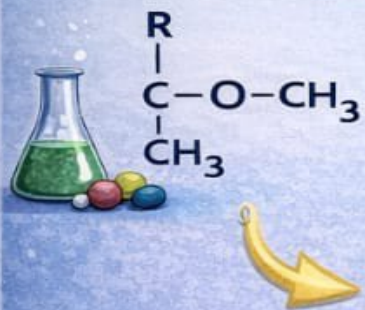
TYPES OF TAFTS STERIC CONSTANT

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

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

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

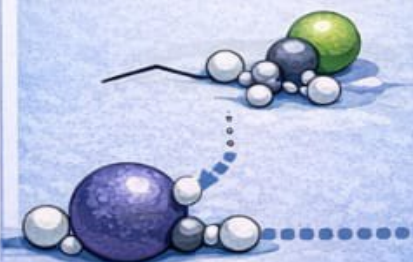


E_s^{max}

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

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

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

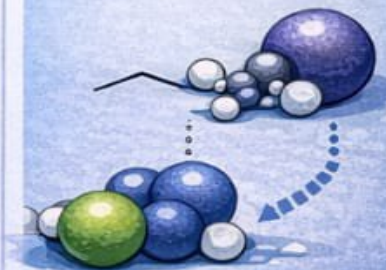


E_s^{old}

$$E_{s^{old}} = -1.0 \log \left(\frac{K_s}{K_H} \right)$$

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

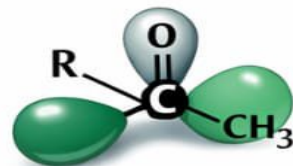
$$E_{s^{old}} = 1.0$$



COMPARISON

Taff Steric vs. Hammett Constant

Taft Steric Parameter (E_s)



Steric Effects



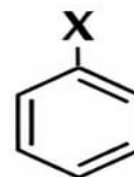
Small Group
(Low E_s)



Large Group
(High E_s)



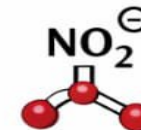
Hammett Constant (σ)



Electronic Effects



Electron-Donating
(Negative σ)

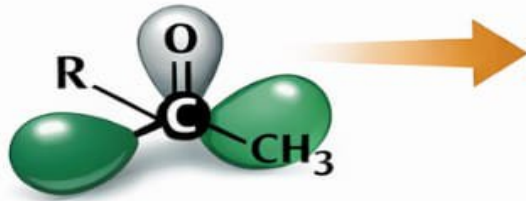


Electron-Withdrawing
(Positive σ)



ROLE OF TAFTS STERIC CONSTANT IN QSAR

Taft Steric Parameter (E_s)



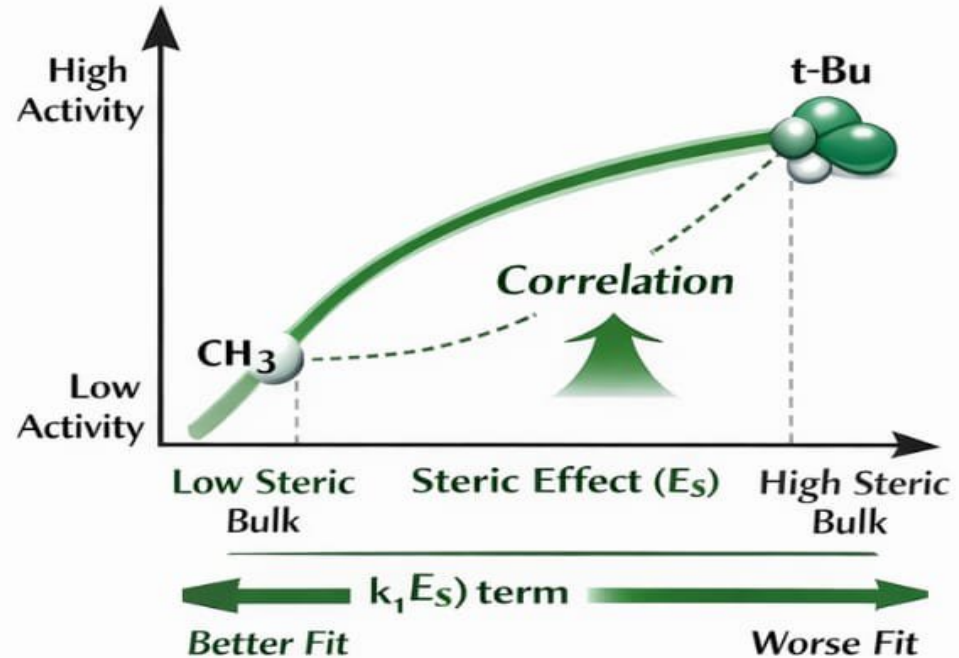
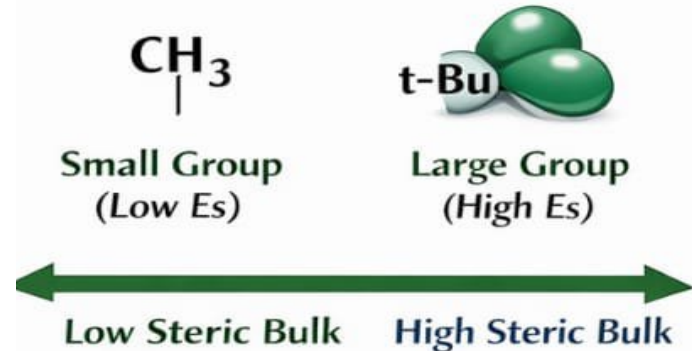
In QSAR Studies: 

$$\text{QSAR Equation: Activity} = k_1(E_s) + k_2 + k_3\sigma + \dots$$

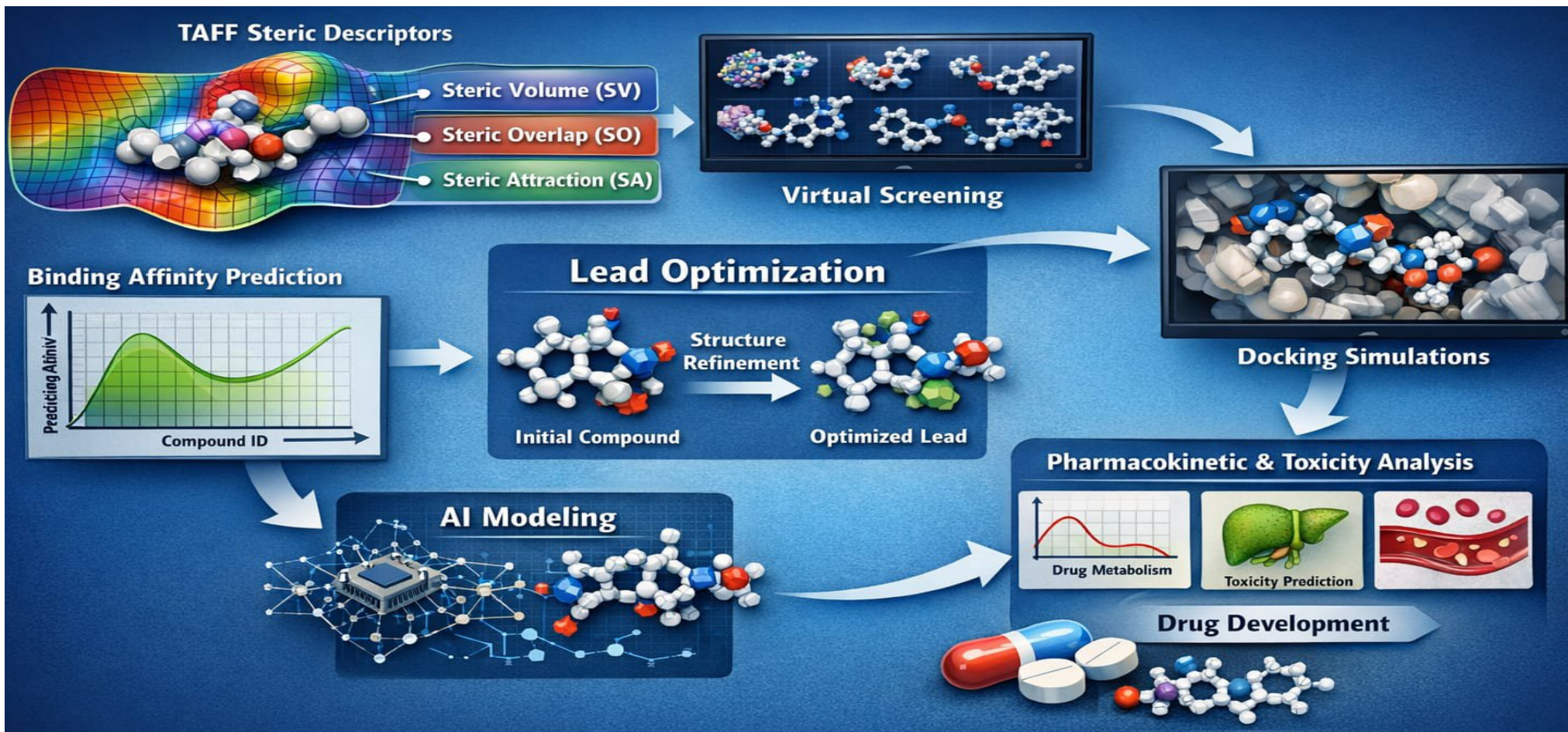
E_s term incorporated into QSAR equations to study steric effects on biological activity

Taft Steric Parameter (E_s)

Measures Steric Effects of Substituents



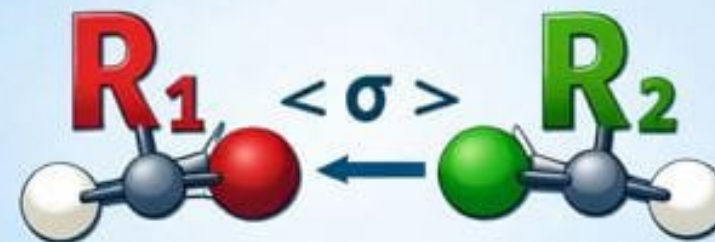
APPLICATIONS OF TAFTS STERIC CONSTANT IN CADD



ADVANTAGES



Measures Steric Effects



Comparing Substituents



Helps in Reaction Analysis

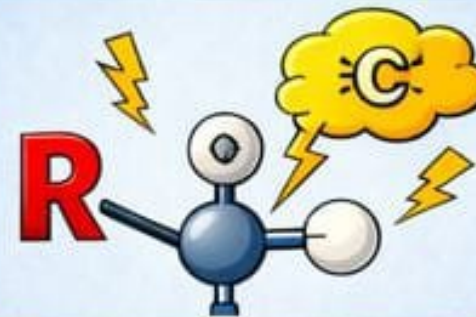


Aids in Molecular Modeling

DISADVANTAGES



Limited Scope



Doesn't Consider Electron Effects



Relative Value



Difficult for Large Molecules

LIMITATIONS OF TAFTS STERIC CONSTANT



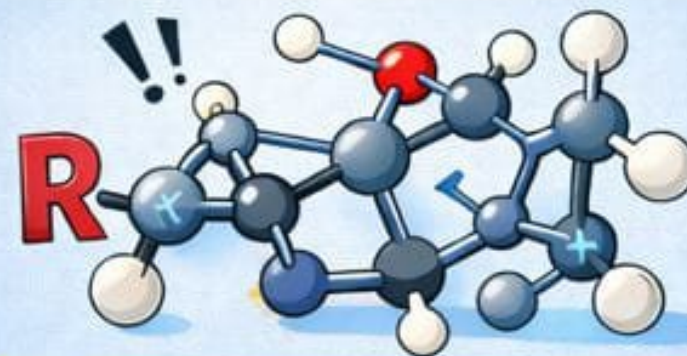
Limited Scope



Too Simplistic



Ignores Electron Effects



Not for Large Molecules

MODERN ALTERNATIVES AND EXTENSIONS

Force Field Refinements



Force Field Refinements

Machine Learning Models



Machine Learning Models

Quantum Mechanics-based Methods



Quantum Mechanics-based Methods

Hybrid Computational Approaches

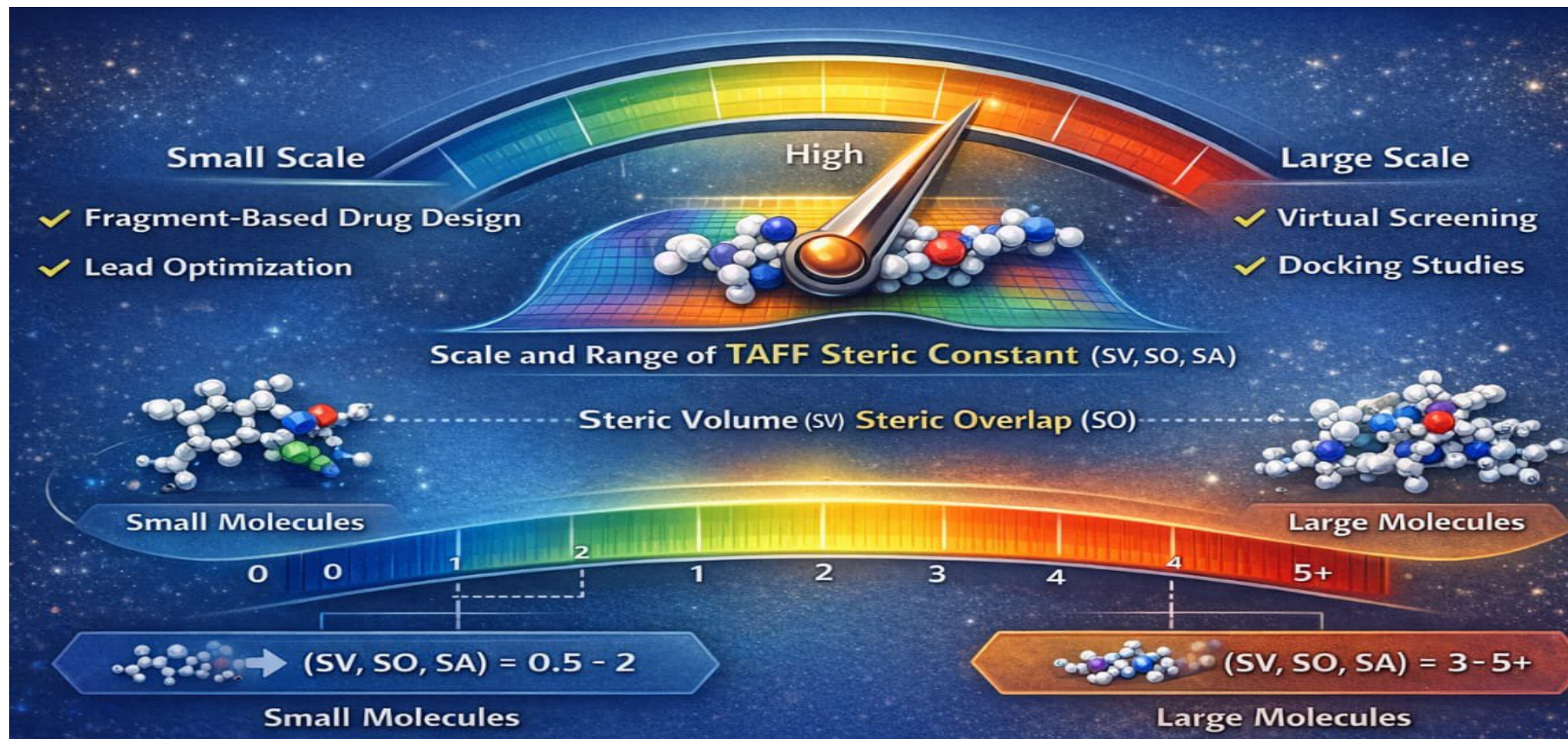


Hybrid Computational Approaches

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



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

