# Performance of Kier-Hall E-states descriptors in QSAR of multi-functional molecules

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# Kier-Hall E-state descriptors

- Pharm.Res. **1990**, 7, 801-807
- JCICS 1991, 31, 76-82
- $I=(\delta^V+1)/\delta$
  - $\delta^V$ and $\delta$ are counts of valence and sigma electrons of atoms associated with the molecular skeleton
- $S_i=I_i+\Delta I_i$
  - E-state value, $S_i$, for skeletal atom I
- $\Delta$Ii, is given as $\Sigma(I_i-I_j)/r_{ij}^2$

# Intrinsic-State Values

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Table I. Intrinsic-State Values

| atom (skeletal hydride group) | intrinsic-state value[a] |
|---|---|
| )C( | 1.250 |
| )CH– | 1.333 |
| $-CH_2-$ | 1.500 |
| )C= | 1.667 |
| $-CH_3$, =CH–, )N– | 2.000 |
| ≡C–, –NH– | 2.500 |
| $=CH_2$, =N– | 3.000 |
| –O– | 3.500 |
| ≡CH, $-NH_2$ | 4.000 |
| =NH | 5.000 |
| ≡N, –OH | 6.000 |
| =O | 7.000 |
| –F | 8.000 |
| –Cl | 4.111 |
| –Br | 2.750 |
| –I | 2.120 |
| =S | 3.667 |
| –SH | 3.222 |
| –S– | 1.833 |

[a] Calculated from eq 2.

# Kier-Hall Atom Types

| RowNo | atom-types-Kier-Hal | RowNo | atom-types-Kier-Hal |
|---|---|---|---|
| 1 | sOH | 19 | ddssS |
| 2 | dO | 20 | sF |
| 3 | ssO | 21 | sCl |
| 4 | aaO | 22 | sBr |
| 5 | sNH2 | 23 | sI |
| 6 | dNH | 24 | sCH3 |
| 7 | ssNH | 25 | ssCH2 |
| 8 | aaNH | 26 | dCH2 |
| 9 | tN | 27 | sssCH1 |
| 10 | dsN | 28 | dsCH1 |
| 11 | aaN | 29 | tCH |
| 12 | sssN | 30 | aaCH |
| 13 | ddsN | 31 | aasC |
| 14 | ssssN+ | 32 | ddC |
| 15 | sSH | 33 | tsC |
| 16 | dS | 34 | dssC |
| 17 | ssS | 35 | ssssC |
| 18 | aaS | | |

# Kier-Hall Algorithm



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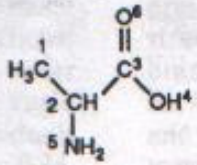
**Table II. Electrotopological-State Calculations for Alanine**

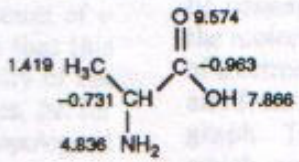



| intrinsic values | intrinsic values | intrinsic values |
|---|---|---|
| $I(1) = 2.000$ | $I(3) = 1.667$ | $I(5) = 4.000$ |
| $I(2) = 1.333$ | $I(4) = 6.000$ | $I(6) = 7.000$ |

$(I_i - I_j)/r_{ij}^2$ Matrix

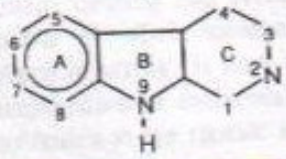
| $i$ \ $j$ | 1 | 2 | 3 | 4 | 5 | 6 | $\Delta I$ = row sum |
|---|---|---|---|---|---|---|---|
| 1 | 0.0 | 0.1667 | 0.0370 | −0.2500 | −0.2222 | −0.3125 | −0.5810 |
| 2 | −0.1667 | 0.0 | −0.083 | −0.5185 | −0.6667 | −0.6296 | −2.0648 |
| 3 | −0.0370 | 0.0833 | 0.0 | −1.0833 | −0.2593 | −1.3333 | −2.6296 |
| 4 | 0.2500 | 0.5185 | 1.0833 | 0.0 | 0.1250 | −0.1111 | 1.8657 |
| 5 | 0.2222 | 0.6667 | 0.2593 | −0.1250 | 0.0 | −0.1875 | 0.8356 |
| 6 | 0.3125 | 0.6296 | 1.3333 | 0.1111 | 0.1875 | 0.0 | 2.5741 |
| | | | | | | | 0.0000 |

$$S_i = I_i + \Delta I_i$$



# QSAR example 1

**Table 6.** Binding of beta-carbolines to the benzodiazepine receptor and electrotopological state values

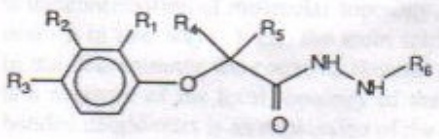



| Obs | $R_1$ | $R_3$ | $R_4$[a] | $R_5$ | $R_6$ | $R_7$ | S(CO)[b] | S(NN) | $S(C_{14})$ | $pIC_{50}$[c] | Calc[d] | Res[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $CH_3$ | H | H | oH | H | H | 0.930 | 3.828 | 1.555 | −0.450 | −1.166 | 0.716 |
| 2 | $CH_3$ | H | H | H | H | $OCH_3$ | 0.921 | 3.831 | 1.523 | −1.980 | −1.228 | −0.752 |
| 3 | $CH_3$ | H | H | H | H | OH | 0.902 | 3.748 | 1.480 | −1.900 | −2.505 | 0.605 |
| 4 | H | $CH_2OH$ | H | H | H | H | 4.867 | 3.712 | 1.845 | 1.591 | 1.972 | −0.381 |
| 5 | H | $COOCH_3$ | H | H | H | H | 5.872 | 3.658 | 1.702 | 2.097 | 1.698 | 0.399 |
| 6 | H | $COOC_2H_5$ | H | H | H | H | 5.997 | 3.688 | 1.719 | 2.155 | 2.277 | −0.122 |
| 7 | H | $COOC_3H_7$ | H | H | H | H | 6.082 | 3.711 | 1.731 | 1.921 | 2.702 | −0.781 |
| 8 | H | $COOCH_3$ | $C_2H_5$ | H | $OCH_3$ | $OCH_3$ | 6.162 | 3.787 | 1.253 | 2.400 | 2.146 | 0.254 |
| 9 | H | $COOC_2H_5$ | $CH_2OCH_3$ | $OCH_2C_6H_5$ | H | H | 6.360 | 3.850 | 1.170 | 2.959 | 2.875 | 0.084 |
| 10 | H | $COOC_3H_5$ | $CH_3$ | O-i$C_3H_7$ | H | H | 6.225 | 3.800 | 1.236 | 2.960 | 2.319 | 0.641 |
| 11 | H | $COONHCH_3$ | H | H | H | H | 5.934 | 3.661 | 1.685 | 1.780 | 1.737 | 0.043 |
| 12 | $CH_3$ | $H_2$ | $H_2$ | H | H | $OCH_3$ | 0.451 | 3.947 | 1.068 | −2.813 | −1.708 | −1.105 |
| 13 | $CH_3$ | $H_2$ | $H_2$ | H | H | OH | 0.434 | 3.864 | 1.023 | −2.748 | −2.969 | 0.221 |
| 14 | H | $COOC_2H_5$ | $CH_2OCH_3$ | H | $OCH_2C_6H_5$ | H | 6.335 | 3.836 | 1.181 | 2.959 | 2.703 | 0.256 |
| 15 | H | H | H | H | H | H | 0.911 | 3.696 | 1.946 | −1.000 | −1.587 | 0.587 |
| 16 | H | H | OOCH | H | H | H | 5.448 | 3.530 | 1.574 | −1.491 | −0.825 | −0.666 |

a. In compounds 12 and 13 the C ring is not aromatic; all others are.
b. $S(CO) = (S(C_3) + S(O))/2$; S(O) is the E-state value for the oxygen attached to the carbon atom in the substituent on position 3. See text. $S(NN) = (S(N_2) + S(N_9))/2$. See text. $S(C_{14}) = (S(C_1) + S(C_4))/2$. See text.
c. The negative log of the $IC_{50}$ value for binding.
d. Calc is the value computed for $pIC_{50}$ from Eq. 9.
e. Res = Calc − $pIC_{50}$.

# QSAR example 2

**Table 5.** Hydrazide monoamine oxidase inhibitors and their electrotopological state values




| Obs | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $S(CH_{14})^a$ | $S(NH_{11})^b$ | $pIC_{50}^c$ | Calc[d] | Res[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | H | H | $CH(CH_3)_2$ | 1.943 | 2.538 | 5.42 | 5.42 | 0.00 |
| 2 | Cl | H | H | H | H | $CH(CH_3)_2$ | 1.926 | 2.515 | 5.60 | 5.66 | −0.06 |
| 3 | H | Cl | H | H | H | $CH(CH_3)_2$ | 1.929 | 2.520 | 5.40 | 5.61 | −0.21 |
| 4 | H | H | Cl | H | H | $CH(CH_3)_2$ | 1.931 | 2.524 | 5.96 | 5.57 | 0.39 |
| 5 | $CH_3$ | H | H | H | H | $CH(CH_3)_2$ | 1.947 | 2.558 | 5.54 | 5.22 | 0.32 |
| 6 | H | $CH_3$ | H | H | H | $CH(CH_3)_2$ | 1.946 | 2.553 | 5.05 | 5.27 | −0.22 |
| 7 | H | H | $CH_3$ | H | H | $CH(CH_3)_2$ | 1.946 | 2.550 | 5.40 | 5.30 | 0.10 |
| 8 | $OCH_3$ | H | H | H | H | $CH(CH_3)_2$ | 1.932 | 2.535 | 5.62 | 5.47 | 0.15 |
| 9 | H | $OCH_3$ | H | H | H | $CH(CH_3)_2$ | 1.934 | 2.536 | 5.42 | 5.45 | −0.03 |
| 10 | H | H | $OCH_3$ | H | H | $CH(CH_3)_2$ | 1.935 | 2.536 | 5.52 | 5.45 | 0.07 |
| 11 | H | H | H | H | $CH_3$ | $CH(CH_3)_2$ | 1.947 | 2.588 | 5.00 | 4.94 | 0.06 |
| 12 | Cl | H | H | H | $CH_3$ | $CH(CH_3)_2$ | 1.930 | 2.565 | 5.16 | 5.19 | −0.03 |
| 13 | H | Cl | H | H | $CH_3$ | $CH(CH_3)_2$ | 1.933 | 2.570 | 4.96 | 5.13 | −0.17 |
| 14 | H | H | Cl | H | $CH_3$ | $CH(CH_3)_2$ | 1.936 | 2.573 | 5.00 | 5.10 | −0.10 |
| 15 | H | H | H | $CH_3$ | $CH_3$ | $CH(CH_3)_2$ | 1.950 | 2.629 | 4.34 | 4.55 | −0.21 |
| 16 | H | H | Cl | $CH_3$ | $CH_3$ | $CH(CH_3)_2$ | 1.938 | 2.614 | 4.80 | 4.71 | 0.09 |
| 17 | H | $CH_3$ | H | H | $CH_3$ | $CH(CH_3)_2$ | 1.951 | 2.603 | 4.90 | 4.79 | 0.11 |
| 18 | H | H | H | H | H | $C_2H_5$ | 1.901 | 2.489 | 5.82 | 5.95 | −0.13 |
| 19 | H | H | Cl | H | H | $C_2H_5$ | 1.889 | 2.474 | 6.00 | 6.12 | −0.12 |
| 20 | H | H | H | H | H | $CH_2C_6H_5$ | 1.103 | 2.587 | 6.14 | 6.44 | −0.30 |
| 21 | H | H | H | H | H | $CH(CH_3)C_6H_5$ | 1.108 | 2.637 | 5.70 | 5.96 | −0.26 |
| 22 | H | H | $CH_3$ | H | H | $CH(CH_3)C_6H_5$ | 1.109 | 2.649 | 6.05 | 5.85 | 0.20 |
| 23 | H | H | $OCH_3$ | H | H | $CH(CH_3)C_6H_5$ | 1.096 | 2.635 | 6.00 | 6.00 | −0.00 |
| 24 | H | H | Cl | H | H | $CH_2C_6H_5$ | 1.089 | 2.573 | 6.96 | 6.60 | 0.36 |

a. $S(CH_{14})$ is the E-state value for the first carbon in the substituent $R_6$.
b. $S(NH_{11})$ is the E-state value for the NH adjacent to the carbonyl group of the hydrazide funtional group.
c. $pIC_{50}$ is the negative log of the inhibitory power $IC_{50}(\mu M)$.
d. Calc is the calculated activity ($pIC_{50}$) from Eq. 8.
e. Res. = $pIC_{50}$ − Calc.

# What to assign as E-sate value of the atom type not present?

- E-state value of ‘0’ is valid result so reporting value of ‘0’ for missing atom type should not be used (as in C2 – Accelyrs)
- Use of –999 as E-state value for missing atom types as input for QSAR

# What are the issues with E-states and multi-functional molecules?

- 35 atom types that are the bases for calculating K-H E-sates are too general
- When dealing with QSAR for datasets where atom-by-atom matching is not possible and any given atom type hit more than once → the result is ambiguity that no statistical tool will resolve

# More on ambiguity

- For example: ssNH could be part of
  - Sulphonamide, RNHSO2R and
  - Amine, RNHR
  - Same atom type, both part of the same molecule – but in very different chemical environment
- What to calculate?
  - An average
  - Sum or
  - Both – the sum and the average

# Testing hypothesis that simple counts should do at least as good as information rich K-H E-states

- Develop the program that will read in the same atom types and do the counts
- Choose several datasets that from QSAR area that feature multi functional type of molecules
- Use the same statistical approach to compare the performance of two sets of descriptors

# Protocol used for comparison

- Descriptors:
  - E-state
    - 35 descriptors based on average E-state values
    - 35 descriptors based on sum of E-states
  - Counts
    - 35 based on the counts of K-H –state atom types
- Datasets
  - logP*, aqueous solubility, Human Intestinal Absorption and Blood Brain Barrier
- Statistical Tools
  - PCA/PLS in Simca (Umetrics)

# Smarts Definitions for Kier-Hall Atom Types

| RowNo | smarts-definitions | estates-atom-types-KH | RowNo | smarts-definitions | estates-atom-types-KH |
|---|---|---|---|---|---|
| 1 | [OH1][*] | sOH | 19 | S(=[*])(=[*])([*])[*] | ddssS |
| 2 | O=[*] | dO | 20 | [F][*] | sF |
| 3 | [OH0]([*])[*] | ssO | 21 | [Cl][*] | sCl |
| 4 | [o] | aaO | 22 | [Br][*] | sBr |
| 5 | [NH2][*] | sNH2 | 23 | [I][*] | sI |
| 6 | [NH1]=[*] | dNH | 24 | [CH3][*] | sCH3 |
| 7 | [NH1]([*])[*] | ssNH | 25 | [CH2]([*])[*] | ssCH2 |
| 8 | [nH1] | aaNH | 26 | [CH2]=[*] | dCH2 |
| 9 | N#[*] | tN | 27 | [CH1]([*])([*])[*] | sssCH1 |
| 10 | [ND2](=[*])[*] | dsN | 28 | [CH1](=[*])[*] | dsCH1 |
| 11 | [nH0] | aaN | 29 | [CH1]#[*] | tCH |
| 12 | N([*])([*])[*] | sssN | 30 | [cH] | aaCH |
| 13 | N(=[*])(=[*])[*] | ddsN | 31 | [cH0] | aasC |
| 14 | [N;+]([*])([*])([*])[*] | ssssN+ | 32 | C(=[*])=[*] | ddC |
| 15 | [SH1][*] | sSH | 33 | C(#[*])[*] | tsC |
| 16 | S=[*] | dS | 34 | C(=[*])([*])[*] | dssC |
| 17 | [SX2]([*])[*] | ssS | 35 | C([*])([*])([*])[*] | ssssC |
| 18 | [s] | aaS | | | |

# Calculating E-state Descriptors

| Name | %F (HIA) | sOH-sum | sOH-av | dO-sum | dO-av | ssO-sum | ssO-av | aaO-sum |
|---|---|---|---|---|---|---|---|---|
| raffinose | 0.3 | 108.94 | 9.9 | -999 | -999 | 26.46 | 5.29 | -999 |
| lactulose | 0.6 | 76.52 | 9.56 | -999 | -999 | 15.31 | 5.1 | -999 |
| aztreonam | 1 | 18.06 | 9.03 | 57.84 | 11.57 | 4.92 | 4.92 | -999 |
| ceftriaxone | 1 | 9.89 | 9.89 | 62.29 | 12.46 | 4.74 | 4.74 | -999 |
| cefuroxime | 1 | 9.5 | 9.5 | 47.57 | 11.89 | 9.3 | 4.65 | 5.13 |
| kanamycin | 1 | 70.91 | 10.13 | -999 | -999 | 22.2 | 5.55 | -999 |

# Counts of Kier-Hall Atom Types

| Name | %F (HIA) | sOH | dO | ssO | aaO | sNH2 | dNH | ssNH | aaNH |
|---|---|---|---|---|---|---|---|---|---|
| raffinose | 0.3 | 11 | 0 | 5 | 0 | 0 | 0 | 0 | 0 |
| lactulose | 0.6 | 8 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| aztreonam | 1 | 2 | 5 | 1 | 0 | 1 | 0 | 1 | 0 |
| ceftriaxone | 1 | 1 | 5 | 1 | 0 | 1 | 0 | 1 | 1 |
| cefuroxime | 1 | 1 | 4 | 2 | 1 | 1 | 0 | 1 | 0 |
| kanamycin | 1 | 7 | 0 | 4 | 0 | 4 | 0 | 0 | 0 |

# Objectives

- Compare quality of the models ($R^2$), based on training set alone and using in-built cross-validation $Q^2$ (LMO) within Simca
- Each of the datasets used has been analysed in the literature using similar approaches but with different descriptors
- NOT designed to build best models for those datasets

# Performance of E-states vs Counts using Simca and PLS

| e-states (ES) | counts of ES at-type | Performance | |
|---|---|---|---|
| $R^2$ | $R^2$ | $(R^2(ES)-R^2(Counts))*100$ | |
| 0.655 | 0.659 | -0.4 | |
| 0.306 | 0.49 | -18.4 | |
| 0.611 | 0.59 | 2.1 | |
| 0.42 | 0.718 | -29.8 | |

# Conclusions

- Simple counts of the same atom types that Kier-Hall Estate descriptors are built on work at least as good in building the models for BBB and solubility, and outperform E-states when building models for HIA and logP, 18% and 30% respectively
- Reviewing recently submitted paper on modelling aqueous solubility, authors made the following observation:
  - Replacing E-states values by binary presentation of the K-H atom types, 1 if present and 0 if not did make much difference in model performance

# Acknowledgment


- Thanks to Daylight for supplying programming toolkits for coding E-states algorithm and development of software for counting atom types based on smarts definitions