The Hydrophobicity of Purine Nucleoside Analogs

Evidence from Partition Coefficients for Conformations with Internal Hydrogen Bonds & Tautomers

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Nucleosides

- 'CONSTRUCTIONIST' approach in CLOGP focuses attention on interaction factors
- CLOGP performed well on sugars, nucleic acids, & pyrimidine nucleosides
- ...but poorly on 84 purine nucleosides and their analogs
- Standard Error four times that of over 10,000 others in Starlist

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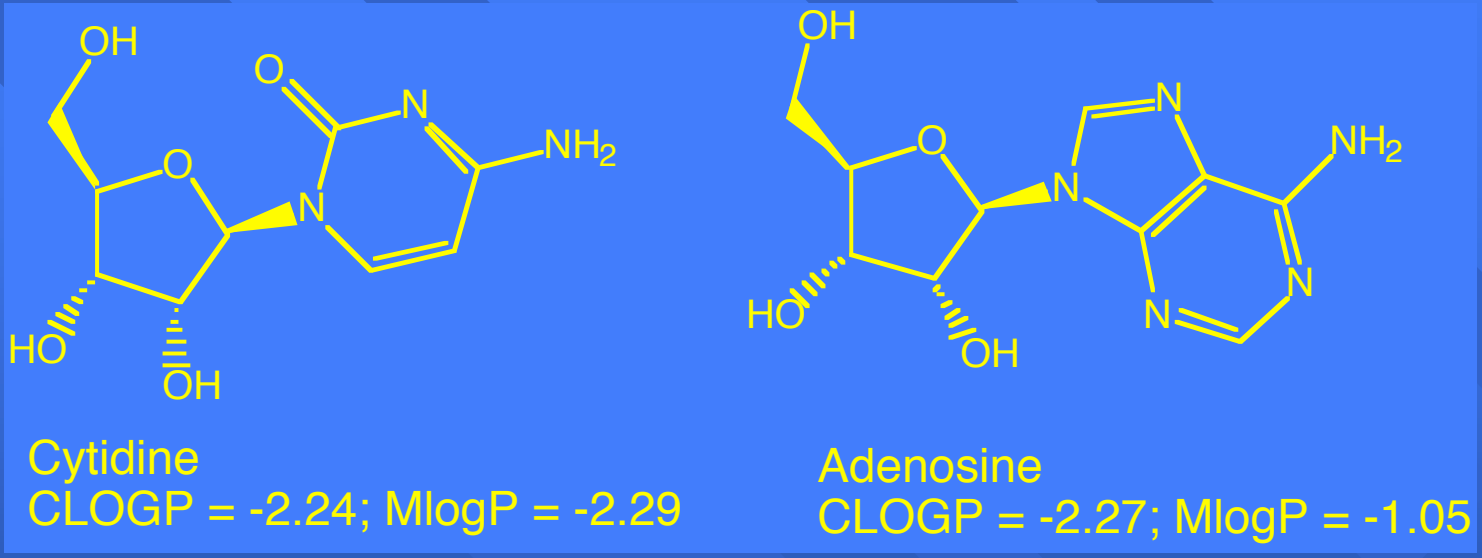
Nucleosides



- Joining the sugar to nucleic acid **N** needs same proximity correction for each
- Suggests long range interaction present in adenosine but not in cytidine (closest approach of **5'-OH** and **N3** of cytidine is 3.5 Angstoms)
- The 3' & **4' de-oxy** analogs of adenosine still calculate low
- Focus then turns on the **5'-OH**

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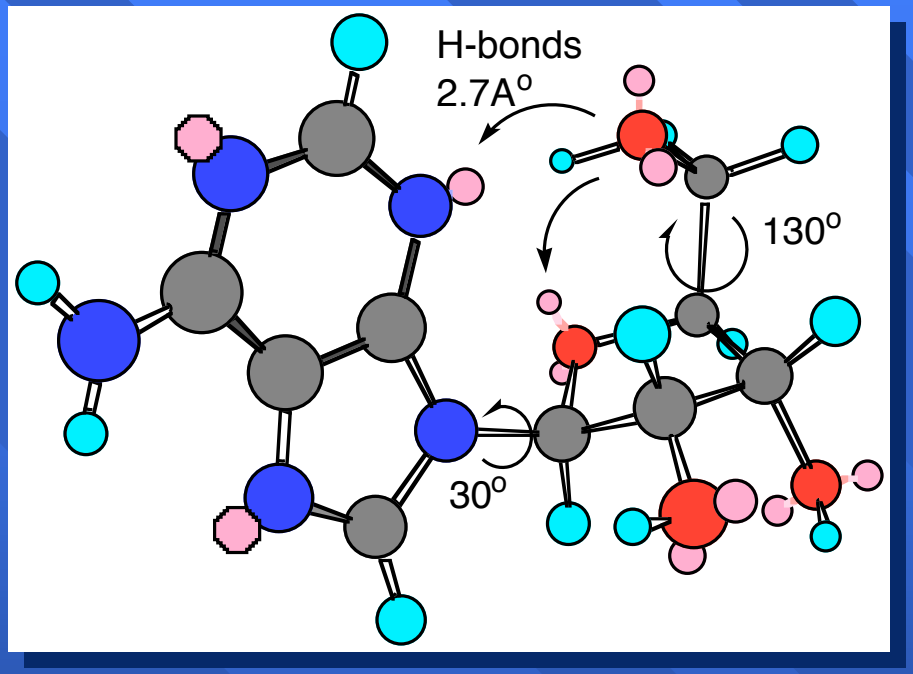
Adenosine, folded



- The bonds attaching the sugar ring to the -CH_2OH and to the purine are freely rotating
- When both are beta, the **5'-OH** can be in ideal distance to H-bond with either **N3** of purine or **O1** of sugar
- The latter already accounted for in YCCY
- H-bond with **N3** strong even though it forms ring of 8 large atoms.
- Needs correction of +0.86 for 84 analogs

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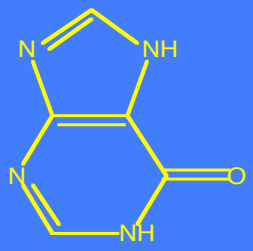
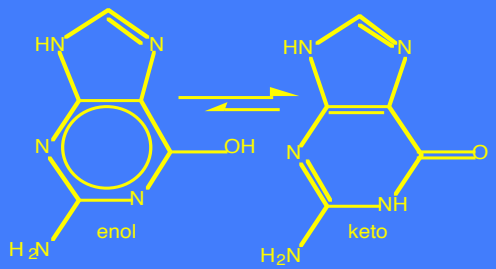
Tautomerism



Hypoxanthine



Guanine

	Hypoxanthine	Guanine
Meas. Log P	-1.11	-0.96
ClogP (keto)	-1.13	-1.16*
ClogP (enol)	+0.49	+0.35

*Average corr. to keto calc. = +0.3

- Amino substituent in guanine shifts equilibrium slightly towards enol
- Same for allopurinol (N moved from 7 to 8);
  Meas. = -0.55; CLOGP = -0.84; $CLOGP^e$ = -0.54

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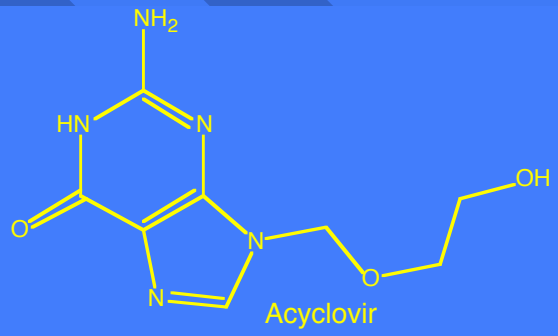
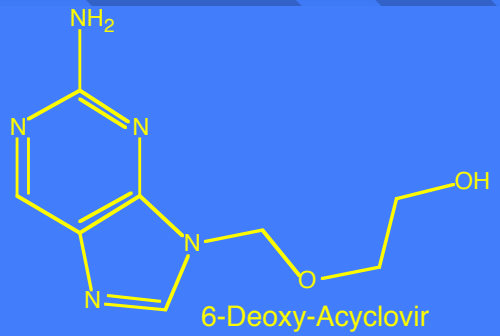
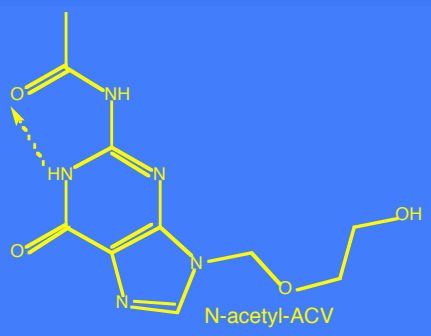
H-bond & Tautomer



Acyclovir



6-Deoxy-Acyclovir



N-acetyl-ACV

	Acyclovir	6-Deoxy-Acyclovir	N-acetyl-ACV
Meas.	-1.56	-1.08	-1.30
ClogP	-1.72*[e] (-2.42)	-1.04* (-1.44)	-1.27* (-1.67)

- *+0.4 for N3-Hbond
- [e] +0.3 for enol portion

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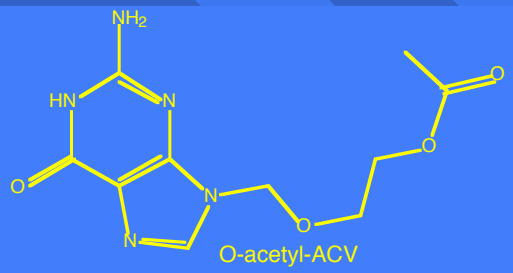
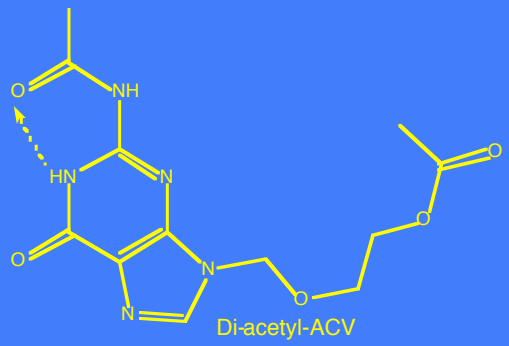
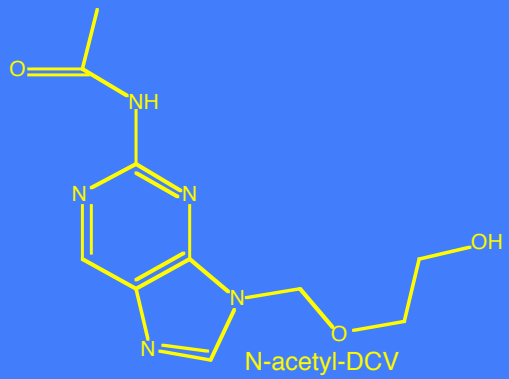
H-Bond & Tautomer



O-acetyl-ACV



Di-acetyl-ACV



N-acetyl-DCV

Meas.	-1.01	-0.85	-1.33
ClogP	-1.23[e] (-1.53)	-0.78	-1.50* (-1.90)

- *+0.4 for N3-Hbond
- [e] +0.3 for enol portion

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Role of Hydrogen Bonding in QSAR

- Hugo Kubinyi asks: "Last mystery in drug design?"
- Log $P_{(oct)}$ has been seen 'deficient' since it is not affected by solute H-donor strength
- Teague & Davis[1] suggest H-bonding much less important in drug-receptor interactions than in the DNA duplex, for example
- Abraham & Mitchell[2] see solute H-donor important in membrane transport, especially BBB.
- H-donor strength measureable by:
  Log P(O/Chl) = - 1.0 V + 3.2 □□ -0.03
  where □□ is 'effective sum of' H-donor strength[3]
- Presently it appears that not enough dependable Log $P_{(Chl)}$ values available, but approach still promising.
- 1) Angew. Chem. Int. Ed., 1999, 38 736-749.
  2) J. Pharm. Sci., 1997, 86, 310-314.
  3) CHEMTECH, July 1996, 20-29

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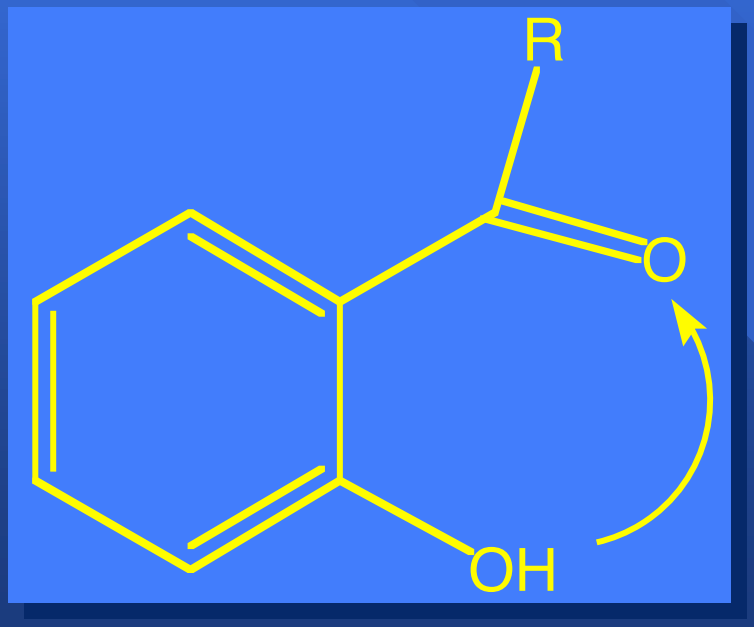
H-Donor Parameter □□

solute	□□
acetic acid	0.59
trichloracetic acid	0.90



R	□□
Me	-0.04
OMe	+0.11
OEt	+0.11
NH_2	+0.58 (0.94*)
OH	+0.86 (0.73*)

*without 2-OH

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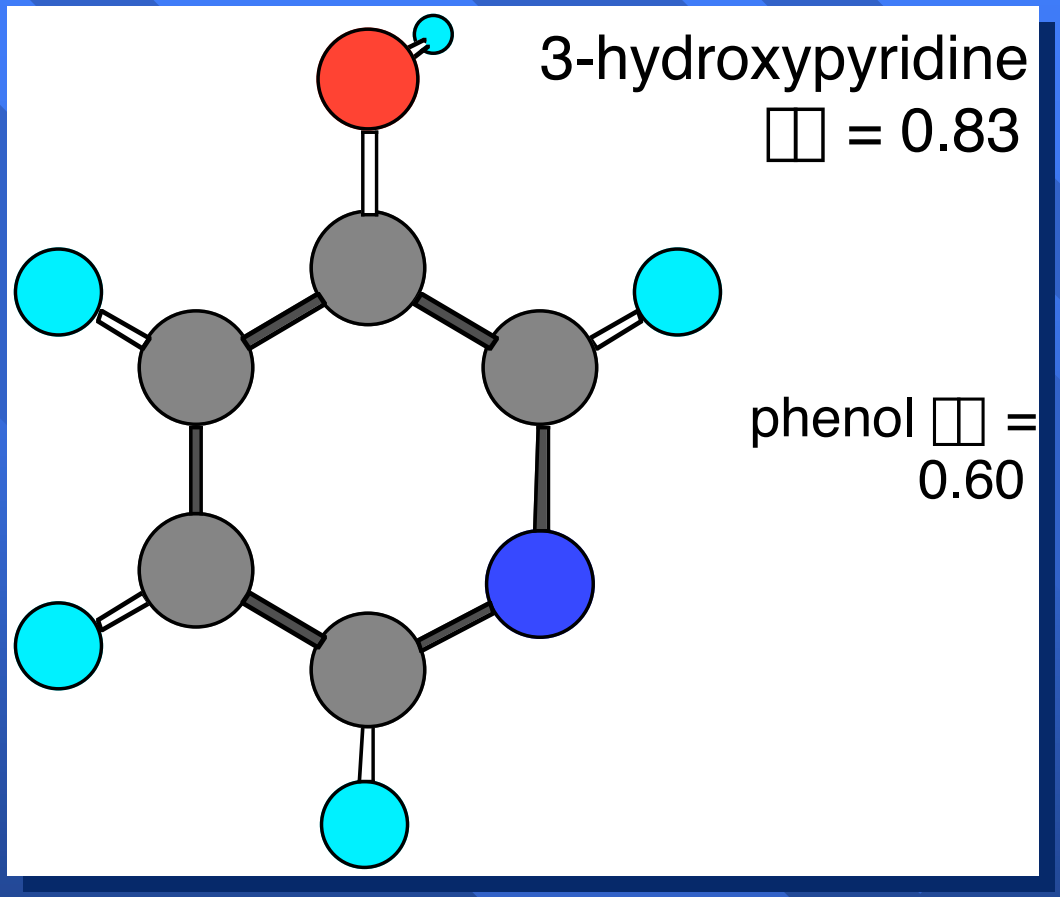
Interactions affecting H-donor strength



- Pyridine **N** two carbons from OH approximately same enhancement as **NO_2** substituent
- Log P(oct) raised by lower □ of oxygen; greater □ not seen..

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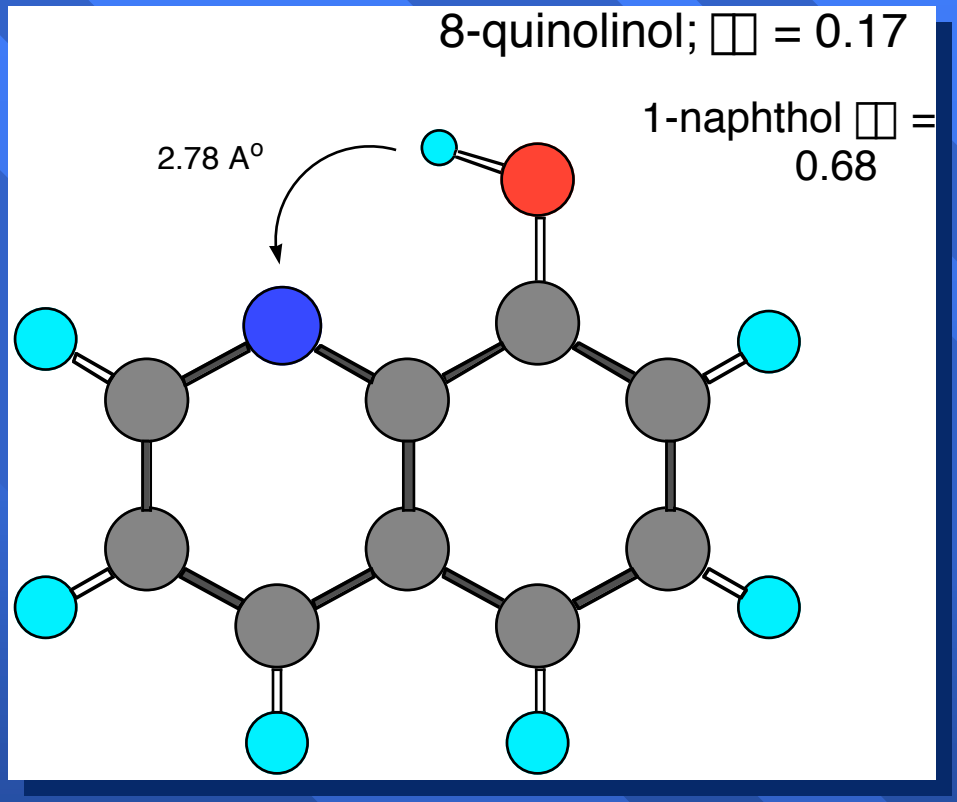
H-bond interactions (cont.)



- Quinoline **N** two carbons from **OH** decreases □□ by 0.51 log units
- Indicates intramol H-bond despite non-optimal angle
- Sigma/rho of 0.65 to 0.70 in ClogP accounts for lower □ of oxygen.

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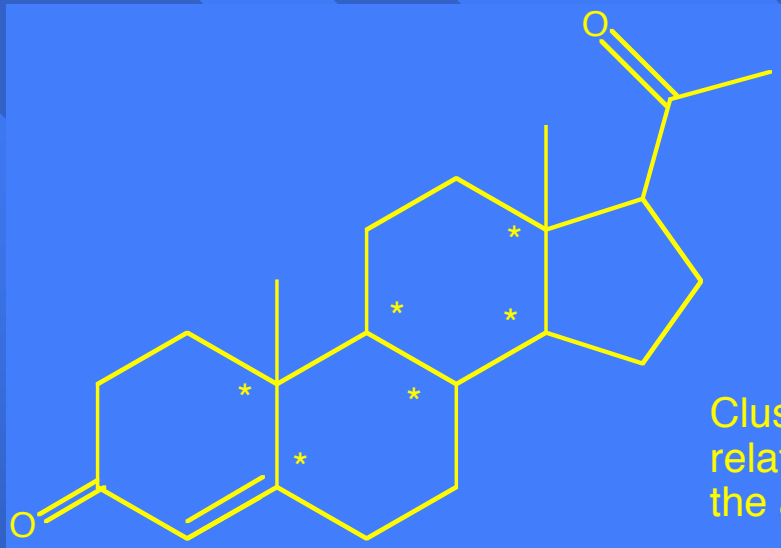
Anomalies



Progesterone: 6 adjacent cluster carbons;
F (clust.brch) = 6(-0.13); CLOGP = 3.77
Meas. = 3.87

Cluster carbons on ring edges creates a relatively flat surface which can accomodate the alkane chain portion of octanol.

- Adjacent cluster carbons join two rings at their edges.
- There are six of these in the common steroids, such as progesterone, resulting in a negative correction for this relatively flat alkane surface.
- Bridged 'cluster carbons' create a cage-like carbon structure. It is tempting to predict that, with less surface per carbon in the 'caged' structure, they should require an even greater negative correction, but on the next slide we show that it is positive.

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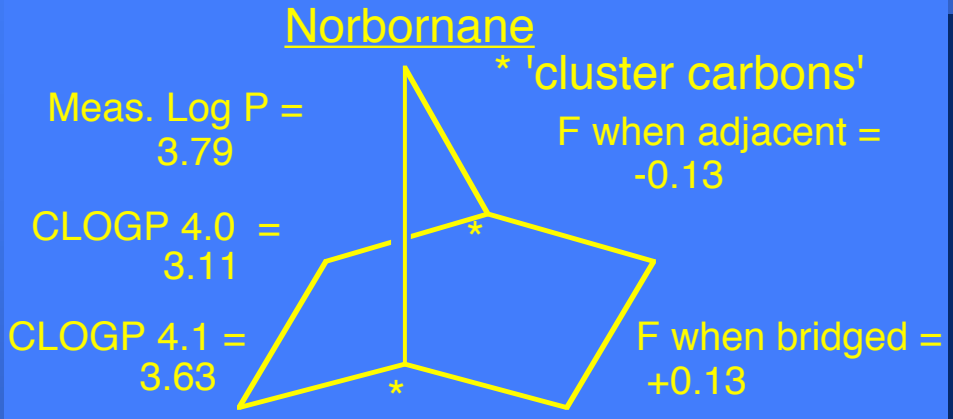
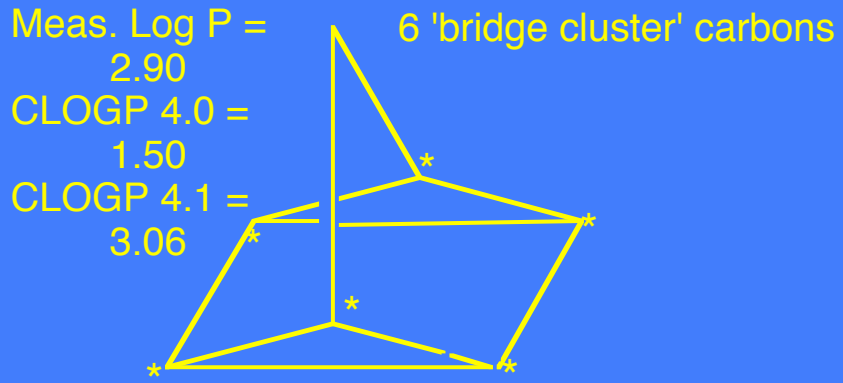
Bridged Cluster Anomaly

Norbornane



Quadricyclane



CLOGP 4.1 recognizes 'bridge cluster' correction

- Bridged 'cluster carbons' create a cage-like carbon structure. It is tempting to predict that the lower surface-to-volume ratio in the 'caged' structure would require an even greater negative correction, while the data show that it is positive.
- Meas. logp Ps 18 analogs from K. Lodge, J.Chem.Eng. Data 1999, 44, 1321-1324. Improves ClogP for aldrin, dieldrin, mirex etc.

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Acknowledgements

- Log P measurements of acyclovir analogs: A. Kristl, J. Chem. Soc., Farad. Trans., 1996, 92, 1721-1724
- To the many post-docs, technicians, and students who, over a period of 35 years, measured partition coefficients in (smelly) octanol, heptane, and (ornery) chloroform, but special thanks to:
- Pricilla Jow
  George Gould
  Gargi Debnath
  Reshma Vasanwalla
- To Michael Medlin (my grandson) who introduced me to PowerPoint