Ab Initio Calculations of a Series of Normal Alcohols for Use in Large-Scale Molecular Dynamics Simulations

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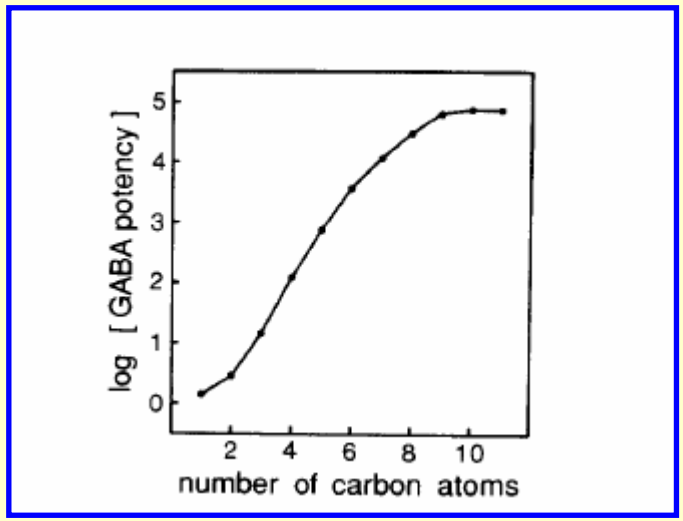
Background

- Effects of alcohol are well known
  - Interactions with the central nervous system cause intoxication
  - Changes in judgment, balance, speech, etc.
- But how?
  - The molecular mechanism by which alcohol produces these effects is unknown

Background

- Cut-off effect
  - The potency of the alcohol molecules increase with increases in alkyl chain length
  - This increase ultimately stops and further additions of methylene groups cause the molecule to produce no effect

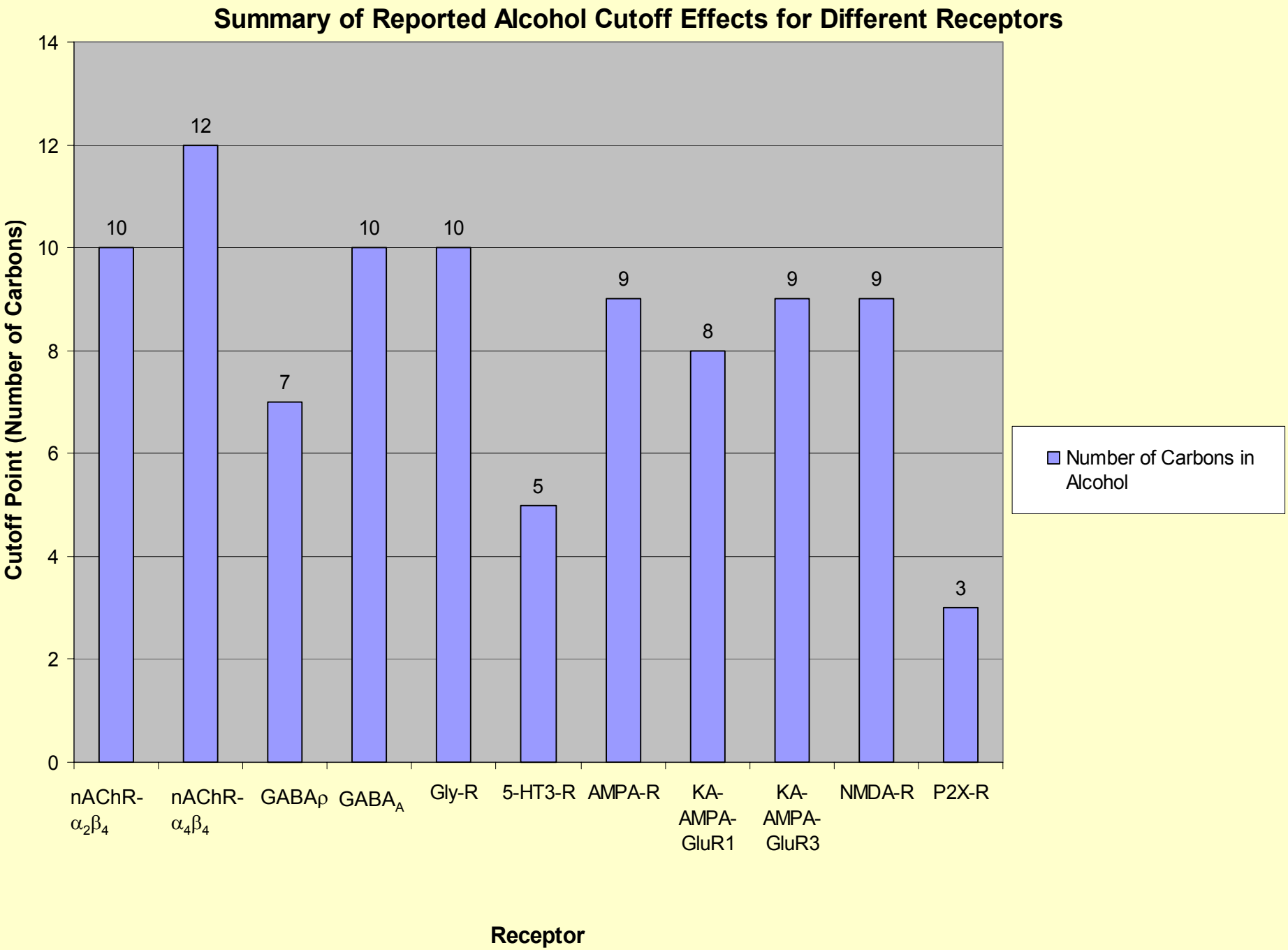


Background

- Current theories:
  - If alcohol acts via a pocket on a ion channel protein, the molecules would eventually become too large for the pocket, thereby excluding longer chain alcohols
  - Increasing alkyl chain length, gradually decreases polarity and hydrophilicity, thus the molecules become less and less soluble in aqueous conditions, and therefore can't reach concentrations necessary to produce the effect

Current Research

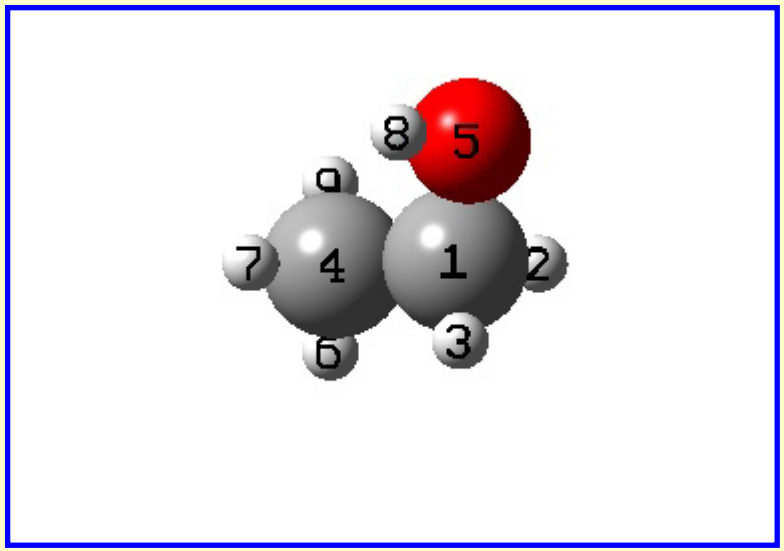
- NMDA glutamate receptor - alcohol cut-off at C_{10}, yet diol cut-off at C_{16}, shows evidence against for molecular volume theory
  - Peoples, R.W. and Hong Ren. *Mol. Pharmacol.* 61:169-176, 2002.
- Voltage-Dependent Ca^{2+} Channels - cut-off at C_{11} - shows that alcohols directly inhibit the function without changing binding dynamics for other molecules
  - Oz, Murat, et. al. *Eur. J. of Pharm*. 418:169-176, 2001.
- GABA-induced Cl^- current increased in rat dorsal root ganglion neurons - cut-off at C_{12}
  - Nakahiro, Masanobu, et. al. *Neuro. Letters.* 205:127-130, 1996.
- AMPA glutamate receptor - cut-off at C_9 - author suggests agreement with alcohol receptor of specific dimensions theory
  - Akinshola, B. Emmanuel. *Brit. J. of Pharm.* 133:651-658, 2001.
- Changes in cut-off values for GABA-R and Gly-R through mutations to a critical part of the channel - evidence backs the specific alcohol binding site
  - Wick, Marilee J. *Proc. Natl. Acad. Sci. USA.* 95:6504-6509, 1998.


Summary of Reported Alcohol Cutoff Effects for Different Receptors
Cutoff Point (Number of Carbons)
0
2
4
6
8
10
12
14
10
12
7
10
10
5
9
8
9
9
3
nAChR-α2β4
nAChR-α4β4
GABAρ
GABAA
Gly-R
5-HT3-R
AMPA-R
KA-AMPA-GluR1
KA-AMPA-GluR3
NMDA-R
P2X-R
Receptor
Number of Carbons in Alcohol

Methods

- Gaussian 98 Program
  - Energy minimization calculations based on electron density and electron positions
- B3LYP/6-311G Basis Set
  - Mathematical description of electron orbitals

Ethanol



Atomic Charges of Geometry-Optimized Ethanol	
Atom/Center Number	**Charge**
C1	-0.10133
H2	0.18822
H3	0.159236
C4	-0.53528
H5	0.172826
H6	0.162612
O7	-0.5872
H8	0.350209
H9	0.190711

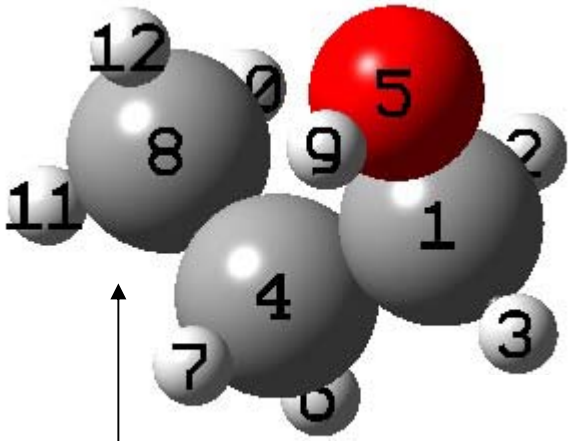
Cartesian Coordinates of Geometry-Optimized Ethanol				
Center Number	**Atomic Number**	**Coordinates (Angstroms (Å))**		
		X	**Y**	**Z**
C1	6	-0.06248	0.570358	0.047403
H2	1	-0.11251	1.280044	-0.77543
H3	1	-0.10951	1.135793	0.985074
C4	6	1.219528	-0.25112	-0.02084
H5	1	2.10182	0.392219	0.025975
H6	1	1.279818	-0.95674	0.812496
O7	8	-1.25577	-0.25611	-0.10975
H8	1	-1.31109	-0.89752	0.620502
H9	1	1.25532	-0.82036	-0.94998

Ethanol

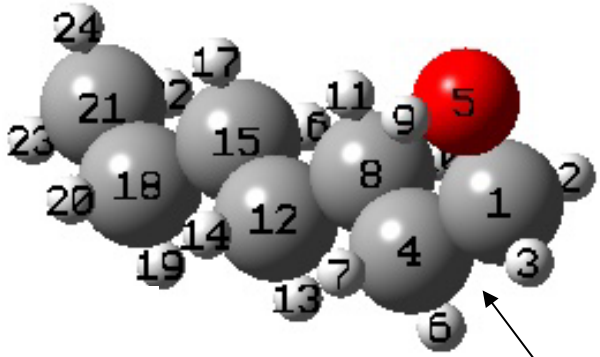
Bond Lengths of Geometry-Optimized Ethanol	
Bond	**Angstroms (Å)**
C1,H2	1.0878
C1,H3	1.096
C1,C4	1.5241
C1,O7	1.46
C4,H5	1.0929
C4,H6	1.0936
C4,H9	1.0902
O7,H8	0.9735

Bond Angles of Geometry-Optimized Ethanol	
Bond	**Angles (Degrees)**
H2,C1,H3	107.9755
H2,C1,H4	110.883
H2,C1,O7	104.4955
H3,C1,H4	110.6389
H3,C1,O7	110.4297
C4,C1,O7	112.1818
C1,C4,H5	111.0902
C1,C4,H6	111.1007
C1,C4,H9	110.3154
H5,C4,H6	107.6169
H5,C4,H9	108.5025
H6,C4,H9	108.1023
C1,O7,H8	109.7955

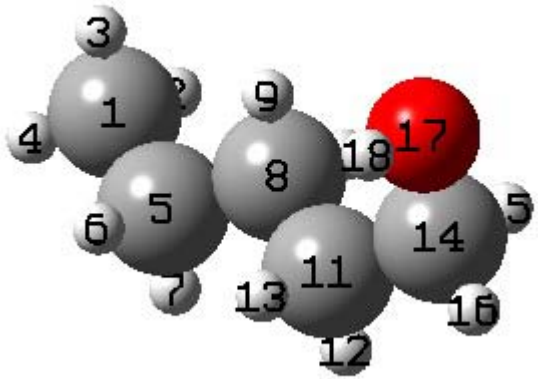
Dihedral Angles of Geometry-Optimized Ethanol	
Bond	**Dihedral Angles(Degrees)**
H2,C1,C4,H5	59.4739
H2,C1,C4,H6	179.2436
H2,C1,C4,H9	-60.8888
H3,C1,C4,H5	-60.3056
H3,C1,C4,H6	59.4642
H3,C1,C4,H9	179.3317
O7,C1,C4,H5	175.8889
O7,C1,C4,H6	-64.3414
O7,C1,C4,H9	55.5261
H2,C1,O7,H8	-177.246
H3,C1,O7,H8	-61.3685
C4,C1,O7,H8	62.5539



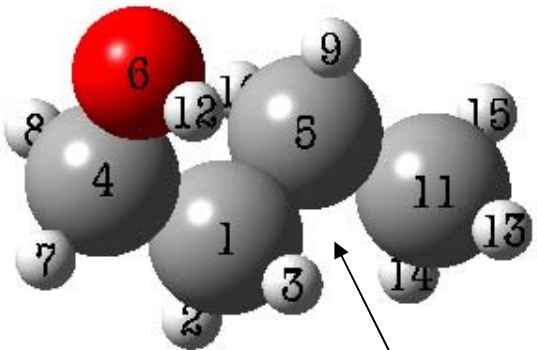
Propanol



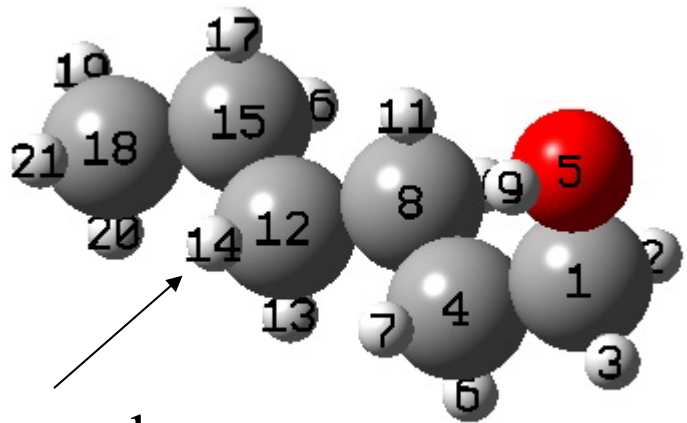
Heptanol



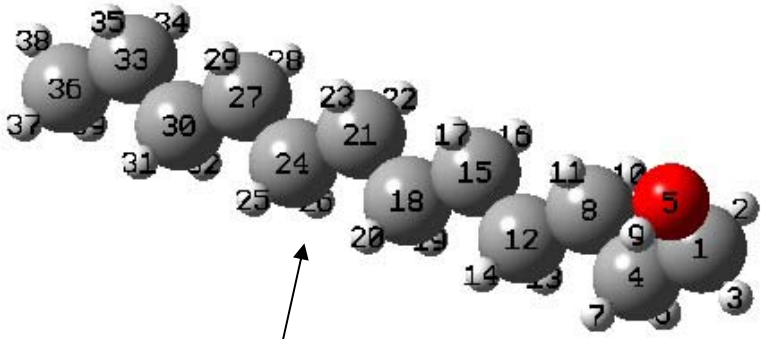
Pentanol



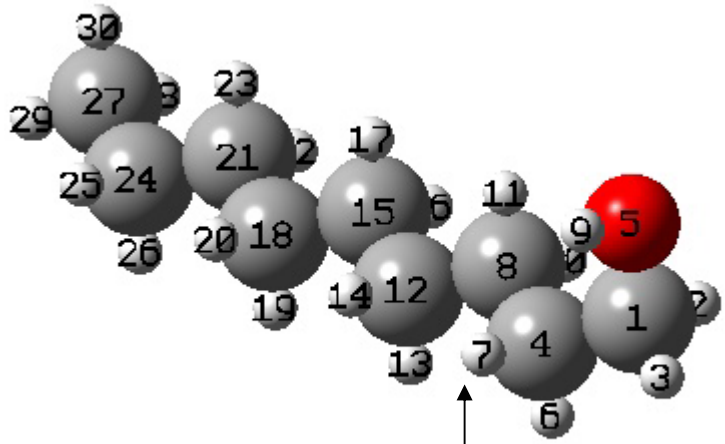
Butanol



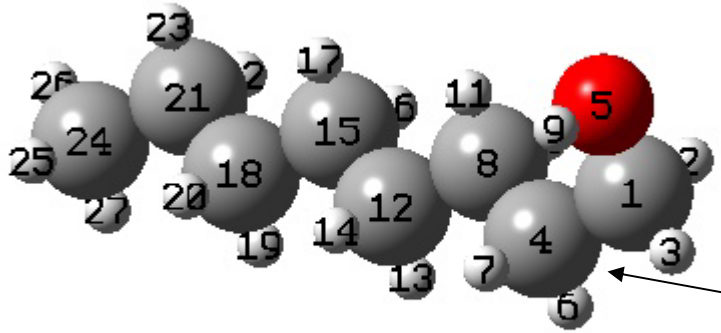
Hexanol



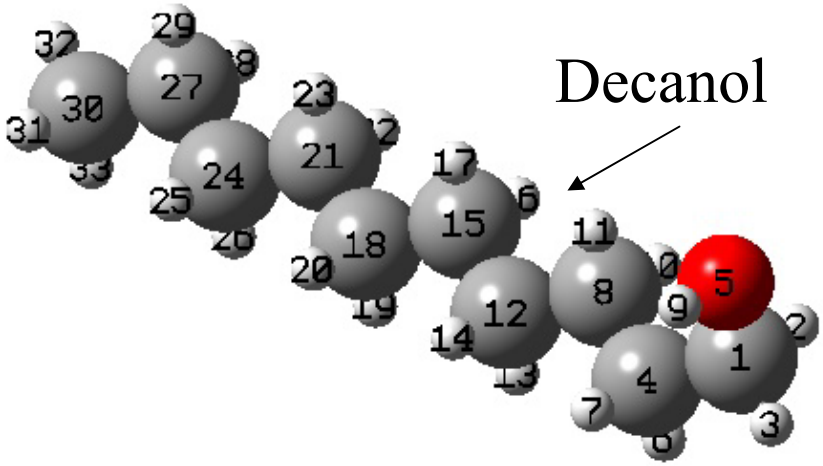
Dodecanol



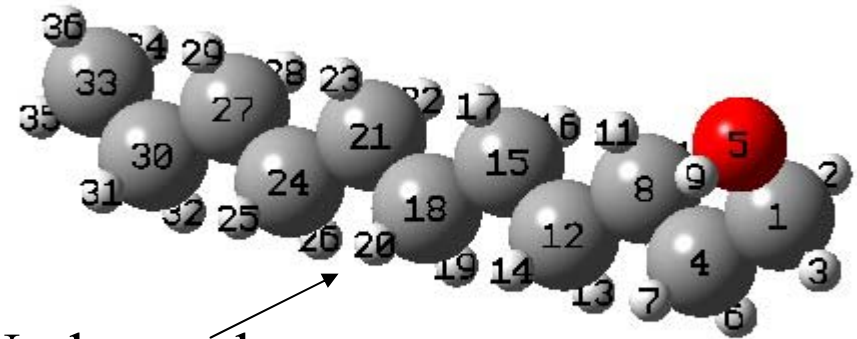
Nonanol



Octanol



Decanol



Undecanol

Dipole Moments

Dipole Moments of Geometry-Optimized n-Alcohols (Debye)		
Molecule	**Gaussian98 Calculated**	**Experimental[1]**
Ethanol	2.06	1.65-1.71
Propanol	2.00	1.55-1.68
Butanol	1.92	1.63-1.69
Pentanol	1.96	1.70-1.71
Hexanol	1.90	1.55-1.65
Heptanol	1.95	1.67-1.73
Octanol	1.89	1.65-1.76
Nonanol	1.95	1.61-1.72
Decanol	1.89	1.62-1.71
Undecanol	1.95	1.67
Dodecanol	1.89	1.52-1.70

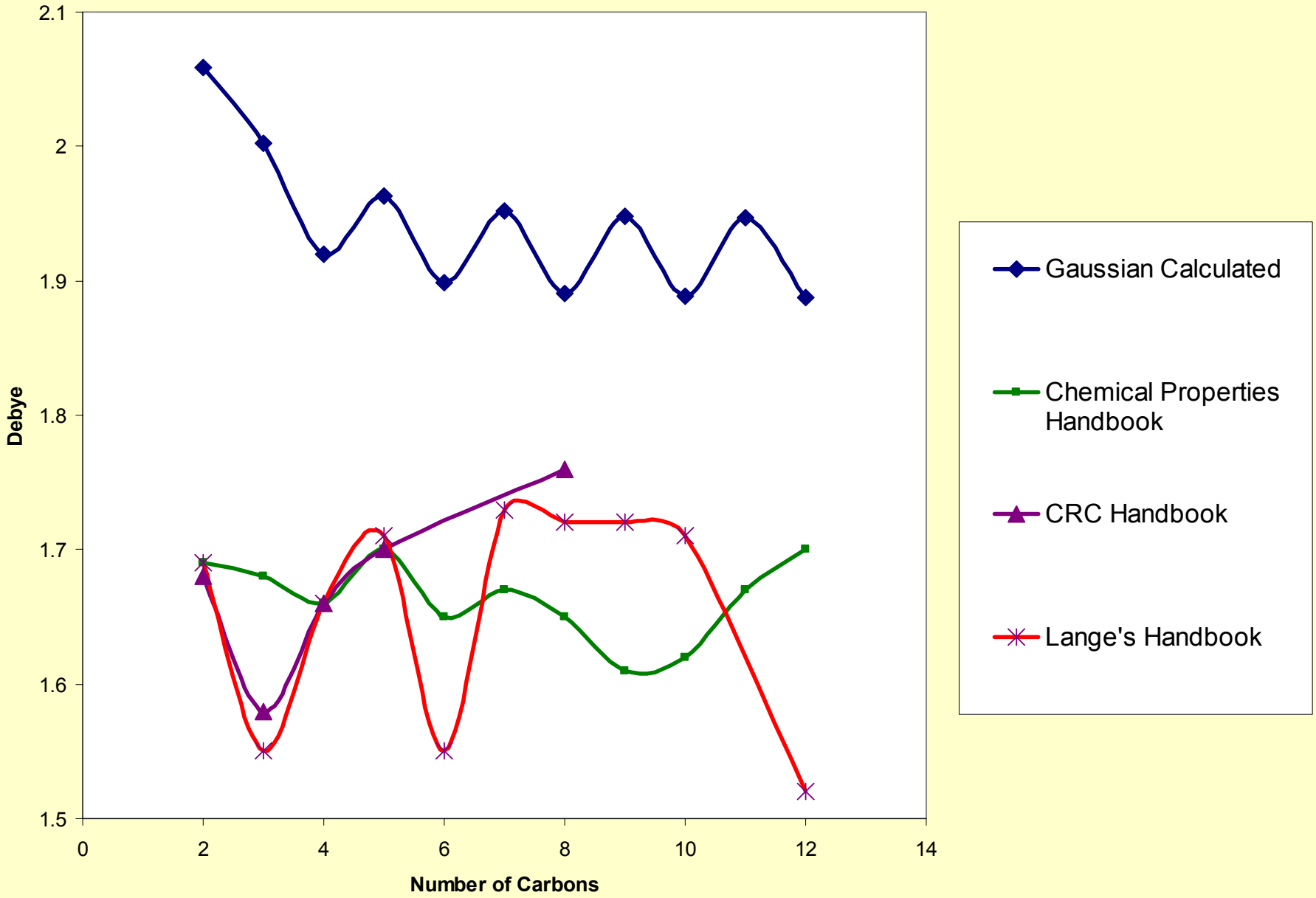
[1] Dipole ranges taken from:

Chemical Properties Handbook. McGraw-Hill, 1999.

Lange's Handbook of Chemistry (15th Edition), 1999.

CRC Handbook of Chemistry and Physics (3rd Electronic Edition), 2000.

Dipole Moments of Geometry-Optimized n-Alcohols



Molecular Volumes

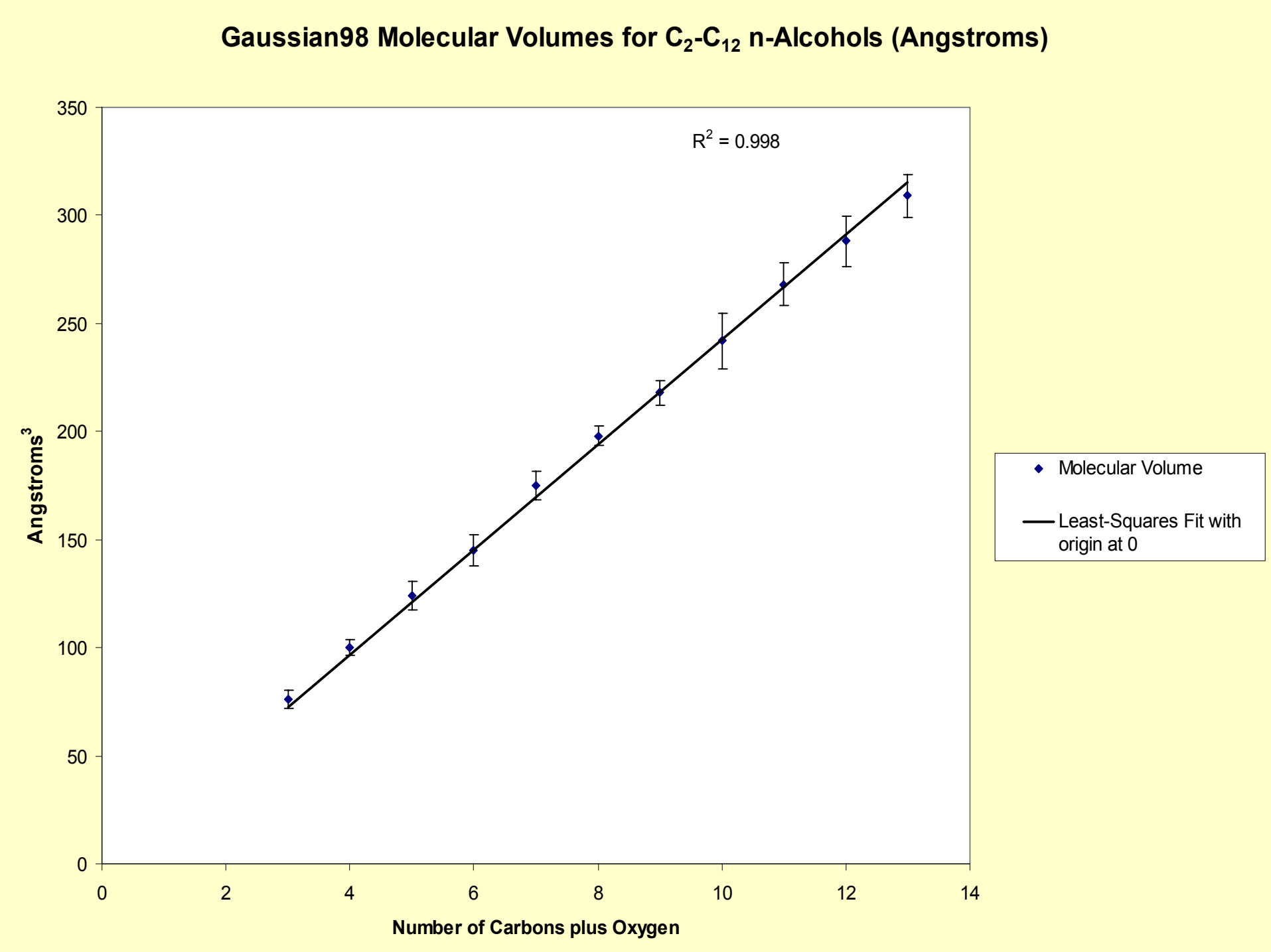
Calculated Molecular Volumes for C_2-C_{12} n-Alcohols (Angstroms)				
	Swiss PDB Viewer	**Gaussian 98**	**Spartan v.5[1]**	**Calculated[2]**
Ethanol	49	76 ± 4	70	97
Propanol	67	100 ± 4	90	125 [25º C]
Butanol	84	124 ± 6	111	152
Pentanol	101	145 ± 7	131	180
Hexanol	118	175 ± 6	152	209
Heptanol	135	198 ± 5	173	235
Octanol	152	218 ± 6	193	262 [25º C]
Nonanol	169	242 ± 13	214	289
Decanol	186	268 ± 10	234	317
Undecanol	202	288 ± 12	258	345
Dodecanol	219	309 ± 10	276	372 [24º C]

[1] Ueno, et. al.: Anesth Analg, Volume 88(4).April 1999.877-883

[2] Volumes based on the equation: (molecular weight/density)/Avogadro's number

Densities from: CRC Handbook of Chemistry and Physics (3rd Electronic Edition), 2000.

Densities taken at 20º C unless otherwise noted.


Gaussian98 Molecular Volumes for C_2-C_{12} n-Alcohols (Angstroms)
R^2 = 0.998
Angstroms^3
Number of Carbons plus Oxygen
0
50
100
150
200
250
300
350
0
2
4
6
8
10
12
14
Molecular Volume
Least-Squares Fit with origin at 0

Discussion and Implications for the Future

- The realm of molecular dynamics simulations has shed new light on complex biological systems
  - Aquaporin water flip
    - Tajkhorshid, Emad et. al. *Science*. 296:525-530, 2002.
  - Anesthetic interaction at the channel-lipid-water inferace
    - Tang, Pei, and Yan Xu. *Proc. Natl. Acad. Sci. USA*. 99:16035-16040, 2002.
- Can lead to new theories and can offer suggestions for further “wet lab” experimentation

Discussion and Implications for the Future

- To be useful and accurate the molecular dynamics simulations require geometry-optimized molecular structures for input as well as other basic molecular parameters

Discussion and Implications for the Future

- This alcohol series can now be used in molecular dynamics simulations to try to make suggestions to answer the questions of:
  - Molecular mechanism, Cut-off effect, etc.

Acknowledgements

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- BBSI