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Chemsketch Study of Phenobarbital: An Antiepileptic Drug

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Abstract: Phenobarbital belongs to the class of medications called barbiturates. It is used to treat insomnia (difficulty sleeping) and as a sedative to relieve the symptoms of anxiety or tension. It is also used for the control of certain types of seizures. It works by slowing down the brain and nervous system. Phenobarbital is a barbiturate, nonselective central nervous system depressant which is primarily used as a sedative hypnotic and also as an anticonvulsant in subhypnotic doses.

Keywords: Phenobarbital, An Anticonvulsant and CNS Activity, ACD/ChemSketch, ACD/3D Viewer

1. Introduction

Phenobarbital belongs to a class of drugs known as barbiturate anticonvulsants/hypnotics [1]- [3]. Barbiturates are substituted pyrimidine derivatives in which the basic structure common to these drugs is barbituric acid, a substance which has no central nervous system (CNS) activity. CNS activity is obtained by substituting alkyl, alkenyl, or aryl groups on the pyrimidine ring. Phenobarbital is chemically Designated as 5-Ethyl -5-phenyl barbituric acid. Phenobarbital (Figure 1) works by controlling the abnormal electrical activity in the brain that occurs during a seizure. This medication is also used for a short time (usually no more than 2 weeks) to help calm you or help you sleep during periods of anxiety [4]- [6].

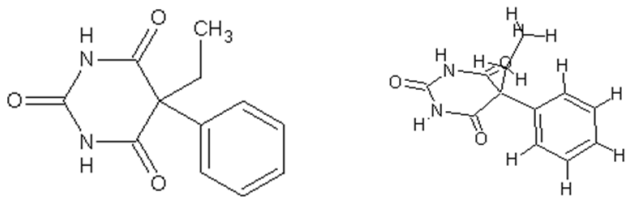

Figure 1. *structure of Phenobarbital.*

1.1. Hypothetical Study of Phenobarbital

ACD/Labs [7]- [9] provides a Chemical Naming Service that will use our powerful software to quickly and accurately name compounds. ACD/Name features enhanced naming capabilities that allow you to generate systematic names according to both IUPAC and CAS Index nomenclature rules, in addition to generating chemical structures from names.

Molecular Formula of Phenobarbital is $C_{12}H_{12}N_2O_3$ and its Molecular Weight is 232.24.

Name of structure 5-ethyl-5-phenylpyrimidine-2,4,6 (1*H*,3*H*,5*H*)-trione.

InChI name of Phenobarbital.

InChI=1S/C12H12N2O3/c1-2-12(8-6-4-3-5-7-8)9(15)13-11(17)14-10(12)16/h3-7H,2H2,1H3, (H2,13,14,15,16,17).

The IUPAC International Chemical Identifier, InChI, was developed as an accurate code to denote the exact configuration of a molecule. With the InChI code, a molecule is unambiguously described by means of its stereochemistry, tautomeric, isotope and electronic charge information [10]- [11]. The IUPAC International Chemical Identifier (InChI) is a textual identifier for chemical substances, designed to provide a standard and human-readable way to encode molecular information and to facilitate the search for such information in databases and on the web. Initially developed by IUPAC and NIST from 2000 to 2005, the format and algorithms are non-proprietary. The current version is 1.04 and was released in September 2011. Prior to 1.04, the software was freely available under the open source LGPL license, but it now uses a custom license called IUPAC-InChI Trust License.

An InChI label is generated by converting an input

chemical structure (in the form of a 'connectiontable') to a unique and predictable set of ASCII characters. The InChI notation is a way of representing chemical compounds in a manner that does not depend on the way of drawing. InChI procedures were developed under IUPAC project during the period 2000–2004. The technical development was carried out primarily at the US National Institute of Standards and Technology (NIST).

1.2. 'Auxiliary Information' (AuxInfo) of Phenobarbital

The InChI Software output complements the Identifier itself with a range of additional information. This includes warnings and errors messages, as well as a specific 'Auxiliary Information' (AuxInfo) string.

AuxInfo[15] contains, in particular, atom non-stereo equivalence information, mapping input atom positions to output positions, and 'reversibility' information for re-drawing the structure. AuxInfo is generated by the inchi-1 executable by default (this behavior may be turned off by using the switch AuxNone). Note that the AuxInfo string itself is a valid input for the inchi-1 generator and may be used to regenerate the source structure.

AuxInfo=1/1/N:13,12,5,4,6,3,7,2,8,9,16,1,14,15,10,11,17/E:(4,5)(6,7)(9,10)(13,14)(15,16)/rA:17CCCCCCCCCOOCCNNCO/rB:s1;s2;d3;s4;d5;d2s6;s1;s1;d8;d9;s1;s12;s8;s9;s14s15;d16;/rC:536,-357,0;691,-268,0;845,-357,0;1000,-268,0;1000,-89,0;845,0,0;691,-89,0;447,-203,0;447,-512,0;536,-48,0;536,-667,0;691,-447,0;691,-625,0;268,-203,0;268,-512,0;179,-357,0;0,-357,0.

1.3. E Molecules

E Molecules is a search engine for chemical molecules. The system was founded by scientists for scientists in 2005 with one goal in mind: reduce drug discovery timelines through improved efficiencies. E molecules of Phenobarbital is given in figure 2.

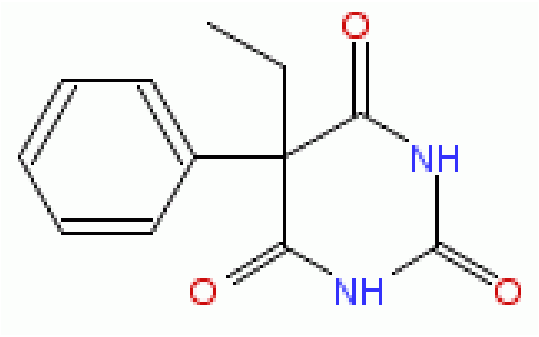

Figure 2. *E molecules of Phenobarbital.*

e molecules of Phenobarbital - Properties
M Wt 232,235
MF $C_{12}H_{12}N_2O_3$
SMILES: CCC1(C(=O)NC(=O)NC1=O)c1ccccc1
CAS: 50-06-6
CAS: 73738-05-3
Name: 5-Ethyl-5-phenyl-pyrimidine-2,4,6-trione

1.4. Smiles Notation of Phenobarbital

The Simplified Molecular-Input Line-Entry System (SMILES) encodes the connectivity of atoms within a compound in an ASCII string, but does not offer 2D or 3D coordinates for molecules.

The simplified molecular-input line-entry system (SMILES) [12]- [13] is a specification in form of a line notation for describing the structure of chemical species using short ASCII strings. SMILES strings can be imported by most molecule editors for conversion back into two-dimensional drawings or three-dimensional models of the molecules. The original SMILES specification was initiated in the 1980s. It has since been modified and extended.Smiles notation of Phenobarbital CCC1(C(=O)NC(=O)NC1=O)c1ccccc1.

1.5. Chemspider of Phenobarbital

ChemSpider is a database of chemicals which is owned by the Royal Society of Chemistry. ChemSpider [14]- [18] is a free chemical structure database providing fast text and structure search access to over 47 million structures from hundreds of data sources. Chemspider structure of Phenobarbital is given in figure 3.

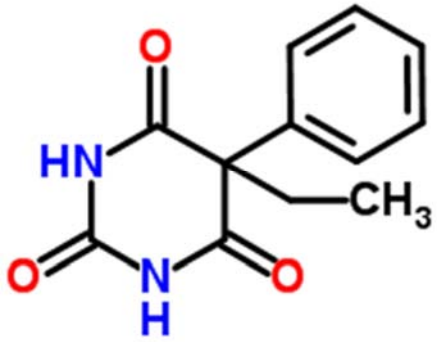

Figure 3. *Chemspider structure of Phenobarbital.*

Chemspider data of Phenobarbital
a) Molecular Formula $C_{12}H_{12}N_2O_3$
b) Average mass 232.235 Da
c) Monoisotopic mass 232.084793 Da
d) Chemspider ID 4599
5-Ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione *[ACD/IUPAC Name]*
2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-ethyl-5-phenyl- *[ACD/Index Name]*

In addition to the drawing capabilities, ACD/ ChemSketch offers predictions of numerous properties for compounds. These include prediction of Molecular formula, Formula weight, Composition, Molar refractivity, Molar volume, Parachor, Index of refraction, Surface tension, Density, Dielectric constant, Polarizability, Monoisotopic, nominal, and average mass.

In this paper, the simple means to calculate these properties and the calculation algorithms are briefly described.

2. Results and Discussions

Algorithms for Calculating Properties

At the heart of the additive-constitutive calculation algorithm of all physicochemical properties in ACD/ChemSketch lies the presumption that these properties can be estimated using additive atomic or group increments [19]. Apart from molecular weight (MW), which is trivial to calculate, the algorithms may be divided into three general groups:

2.1. Basic Macroscopic Properties: Molar Volume (MV), Molar Refractivity (MR), and Parachor (Pr)

2.1.1. Molar Volume, MV

By definition,

$$MV = MW/d$$

ACD/ChemSketch calculates molar volume from additive increments. The additive atomic increments were obtained using a database of density and calculated MW.

2.1.2. Molar Refractivity, MR

The Lorentz-Lorenz equation relates refractive index, density, and refractive index

$$MR = n^2\text{-}1/n^2\text{-}2.\ MW/d$$

ACD/ChemSketch calculates molar refractivity from additive increments. The additive atomic increments were obtained using a database of density, refractive index, and calculated MW.

2.1.3. Parachor, Pr

By definition,

$$P_\gamma = [MW/d]\ \gamma^{1/4}$$

ACD/ChemSketch calculates the parachor from additive increments. The additive atomic increments were obtained using a database of density, surface tension, and calculated MW.

2.2. Derived Macroscopic Properties: Density (d), Refractive Index (n), and Surface Tension (γ)

2.2.1. Density, d

By definition,

$$d = MW/MV$$

ACD/ChemSketch calculates the density from MW and the calculated molar volume (see above).

2.2.2. Refractive Index, n

By the Lorentz-Lorenz equation,

$$n = \sqrt{2.MR + MV/\ MV - MR}$$

ACD/ChemSketch calculates the refractive index from the molar volume and molar refractivity, both of which are calculated as above.

2.2.3. Surface Tension, γ

By definition,

$$\gamma = [\ P_\gamma /MV]^4$$

ACD/ChemSketch calculates the surface tension from calculated MV (see above) and calculated

P*r* (see above).

2.3. The Dielectric Constant ε (Permittivity)

Basic macroscopic properties such as molar volume (MV), molar refractivity (MR), and the parachor (P*r*) are calculated first for the input structure. The atomic additive increments in such an algorithm depend on the bonds (single, double, aromatic, *etc*.) of this atom and on neighboring atoms. ACD/ChemSketch rapidly analyzes the input structure to determine the class of each atom, *i.e.,* whether it is cyclic, aromatic, aliphatic, *etc*. The prediction algorithms for density (*d*), refractive index (*n*) and surface tension (γ) are founded on well-known physicochemical formula which can be found in literature on physicochemical properties of compounds.

They express *d*, *n*, and γ as functions of MV, MR, or P*r*. Once the MV, MR, or P*r*, have been predicted by additive means, it is straightforward to predict *d*, *n*, and γ using these formula.

The determination of the additive-constitutive atomic increments for MV, MR, and P*r* were obtained internally by ACD/Labs scientists using large experimental databases relating structure to density, refractive index, and surface tension. The MV, MR, and P*r* were recalculated from *d*, *n*, and γ. These parameters are proprietary information of ACD/Labs, Inc. The prediction of the dielectric constant ε (permittivity) resembles very closely the prediction of boiling point, which is a separate ACD/Labs product available from ACD/ChemSketch. Senior scientists at ACD/Labs discovered an additive function, which relates the dielectric constant to other macroscopic properties which can be additively treated, such as MV. Once this relationship was discovered, the additive-constitutive atomic increments for this function were obtained using large databases consisting of molecular structures and their observed dielectric constants.

Using the function and estimated MV for the input structure, its dielectric constant can be quickly predicted.

By definition,

$$f(\varepsilon) = f(MV, AdditiveFunction)$$

ACD/ChemSketch calculates the dielectric constant from calculated MV (see above) and a proprietary empirical additive function.

2.4. Polarizability

This property is calculated from the Molar Refractivity (MR) as follows:

$$Polarizability = 0.3964308 \cdot MR$$

2.5. Monoisotopic, Nominal and Average Mass

Monoisotopic mass (Mmi) is the exact mass of the most abundant stable isotope that can occur naturally.

Nominal Mass (Mn) is the sum of the approximated monoisotopic masses of the elements forming the structure.

Average Mass (Mav) is the calculated mass of a particle based on the atomic weights of the elements from which it is comp.

Molecular Formula:	$C_{12}H_{12}N_2O_3$
Formula Weight:	232.23528
Composition:	C(62.06%) H(5.21%) N(12.06%) O(20.67%)
Molar Refractivity:	59.21 ± 0.3 cm 3
Molar Volume:	188.1 ± 3.0 cm 3
Parachor:	482.8 ± 6.0 cm3
Index of Refraction:	1.541 ± 0.02
Surface Tension:	43.3 ± 3.0 dyne/cm
Density:	1.233 ± 0.06 g/cm^3
Dielectric Constant:	Not available
Polarizability:	23.47 ± 0.5 10 -24cm^3
RDBE:	8
Monoisotopic Mass:	232.084792 Da
Nominal Mass:	232 Da
Average Mass:	232.2353 Da
M^+:	232.084244 Da
M^-:	232.085341 Da
$[M+H]^+$:	233.092069 Da
$[M+H]^-$:	233.093166 Da
$[M-H]^+$:	231.076419 Da

The partition constant, *P*, is a measure of the propensity of a neutral molecule to differentially dissolve in two immiscible phases, and serves as a quantitative descriptor of lipophilicity. The log*P* prediction model provides an estimate of the value of the octanol-water partitioning coefficient (also referred to as K_{OW}) as the logarithmic ratio (log*P*) from structure. ACD/Log*P* is used worldwide by chemists in various arms of chemical research, including some of the world's largest pharmaceutical companies (GlaxoSmithKline and Pfizer, to name just a few). Calculated log P of Phenobarbital = 1.67+/- 0.25.

3. 3D Viewer –3D Optimised Forms of Phenobarbital

ACD/3D Viewer is a fast yet accurate 3D modeling and visualization program [20]. It is fully integrated with ACD/ChemSketch, allowing you to draw 2D structures and quickly obtain their 3D representations in a striking 16 color display. With ACD/3D Viewer you can:

a) Manipulate 3D models: move, 2D and 3D rotate, also at a fixed angle, resize, change styles, and colors;
b) Display a 3D structure as stick, ball-and-stick, spheres, or disks;
c) Add an overlay of small-dots at approximately the Van der Waals radius level to the solid 3D structure;
d) Measure and change bond lengths, bond angles, and torsion angles;
e) Optimize the structure using a 3D CHARMM-type of force field;
f) Switch from 3D to 2D display in the ChemSketch window at the click of a button;
g) Set the 3D structure to Auto-rotate, with or without changing the style of structure display;
h) Rotate and move selected atoms rather than entire structures.
i) Change and delete atoms, assign the center of rotation to an atom.
j) Create movies and save them as.GIF files;
k) View 3D structure in perspective; and
l) Export 3D models to other geometry optimization programs and use them as good starting configurations.

The ACD/3D Viewer, being powerfull modeling and visualization program, presents you with various styles of structure 3D representation. The 3D structure can be displayed as wireframe, sticks, sticks with dots, dots only, Ball and sticks, ball and sticks with dots, spacefills, disks, disks with dots forms.The various 3D forms of Phenobarbital are given in figures 4-8.

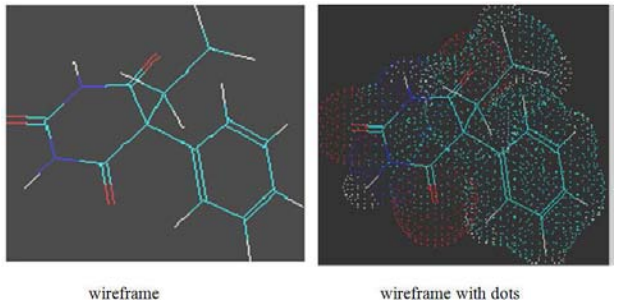

Figure 4. *3D optimized wireframe and wireframe with dots forms of Phenobarbital.*

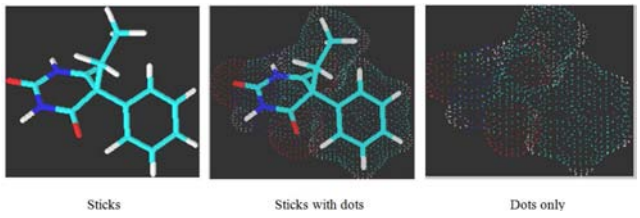

Figure 5. *3D optimized Sticks, Sticks with dots and Dots only forms of Phenobarbital.*

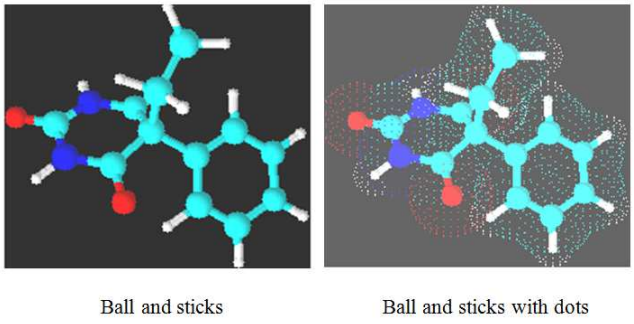

Figure 6. *3D optimized Ball and sticks form and Ball and sticks form with dots of Phenobarbital.*

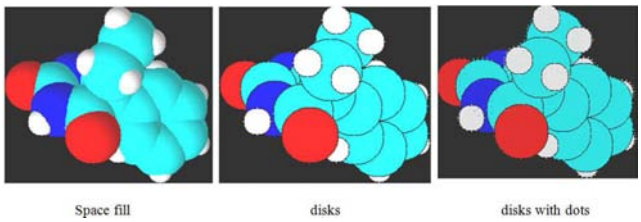

Figure 7. *3D optimized spacefill form, disks form and disks with dots forms of Phenobarbital.*

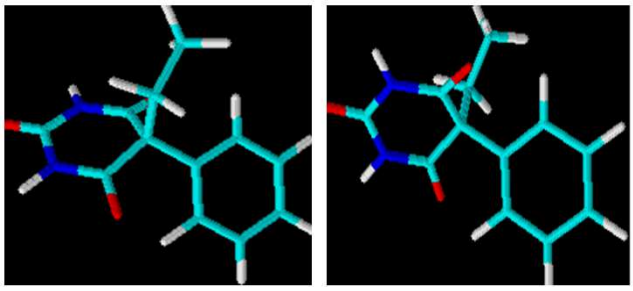

Figure 8. *Mirror images of 3D optimized forms of Phenobarbital.*

4. Conclusion

The chemsketch study of Phenobarbital is informative in understanding various structural and physicochemical aspects of the compound. The ACD/3D Viewer fully integrated with ACD/ChemSketch, helps in visualizing the various styles of structure 3D representation of Phenobarbital.

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