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Electronic structure and dosage correlation of 1,4-benzodiazepines

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ABSTRACT

Density functional theory was used to calculate the electronic structure of 20 selected 1,4-benzodiazepine derivatives. Certain parameters were extracted from the theoretical calculations, including the proton affinity of N1, the total energy, HOMO and LUMO energies, the total positive atomic charge, dipole moment and molecular volume. These parameters were used for the correlation with the minimum effective dose acting on human. The correlation was performed by applying linear least square method. Seven parameters were found to afford good fit. Clorazepate, one of the benzodiazepines, was studied extensively, it contains a carboxylate group, which can act as an ordinary molecule or zwitterions, where the ionisable proton migrates to N1. The energy gap between the two forms was found to be strongly dependent on the solvent dielectric constant.

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1. Introduction

Benzodiazepines are a class of chemical compounds with wide medical applications. They contain a benzene ring fused to a diazepine ring. They are known since 1955, when Dr. Leo Sternbach discovered the drug chlordiazepoxide. The importance of benzodiazepines made them the most prescribed medications [1]. Benzodiazepines primarily used as anxiolytic, some of them can be used as hypnotic. They are known also for muscle relaxant indications. The mechanism of action is through binding with GABA-A (Gama-aminobutyric acid type A) receptor which potentiates GABAergic neurotransmission [2]. Their half-life in human blood may be short, intermediate, or long. Short and intermediate half-lives are preferred for the treatment of insomnia; longer half-life usually used for the treatment of anxiety [3].

Common types of benzodiazepines are i) Keto compounds, where keto oxygen is attached to C3 (Clorazepate, diazepam and flurazepam), ii) Hydroxy group attached to C2 (Lorazepam, lormetazepam and oxazepam), iii) Nitro group attached to C8 (Nitrazepam, flunitrazepam and nimetazepam) and iv) Imidazole fused to N2 and C3 (Climazolam, loprazolam, midazolam) (Figure 1) [4,5].

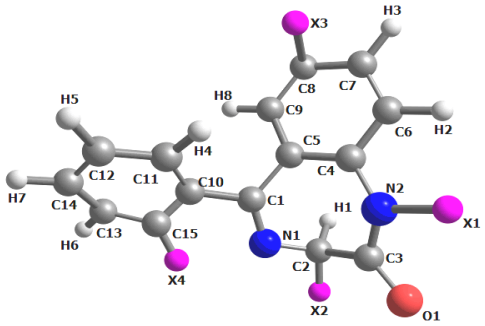

Figure 1. Benzodiazepine nucleus numbering scheme with groups X1, X2, X3 and X4.

There is a discrepancy regarding the minimum effective doses [6-8] of benzodiazepines acting on human. This dose does not calibrate among the different compounds. In this work, we propose a procedure to calculate calibrated doses by connecting the minimum effective dose with certain molecular parameters. From the linear coefficients obtained from applying least square procedure to the linear equation, we can calculate back the proper doses.

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Table 1. Used theoretical parameters and the calculated dose according to Equation (1).

Compound	HOMO	LUMO	D	MV	MM	CT	NA	PA	ET	t½ [a]	Dose [b]	Calc.[c]	Drec.[d]
1	-0.2091	-0.0995	3.95	183	316	0.802	29	251	-91.3	12	3.00	6.94	5.0
2	-0.2244	-0.1084	5.61	212	358	0.923	35	241	-41.6	9	20.00	18.60	20.0
3	-0.2121	-0.1158	7.51	194	315	0.966	32	242	-38.4	18	0.25	3.40	3.0
4	-0.2230	-0.1273	2.39	193	316	0.990	32	239	-38.9	48	10.00	11.40	10.0
5	-0.2111	-0.0986	3.52	198.	304	0.879	30	254	-45.8	60	0.50	0.15	0.5
6	-0.2052	-0.0957	2.63	182	285	0.775	33	244	-34.4	20	5.00	5.93	5.0
7	-0.2066	-0.0968	3.68	199	319	0.909	33	245	-46.9	42	2.00	3.89	5.0
8	-0.2164	-0.1034	5.44	214	349	0.939	38	245	-42.2	3	10.00	9.00	10.0
9	-0.2101	-0.0978	3.37	183	333	0.810	30	254	-93.5	10.6	4.00	3.50	4.0
10	-0.1801	-0.0956	3.54	242	388	1.142	50	247	-43.9	40	15.00	15.00	15.0
11	-0.2055	-0.0949	3.55	219	343	0.960	40	254	-40.2	60	10.00	9.90	10.0
12	-0.2151	-0.1015	3.09	206	353	0.940	36	240	-43.5	14	20.00	11.70	10.0
13	-0.2168	-0.1020	5.02	194	321	0.923	31	244	-47.8	10	1.00	0.47	0.5
14	-0.2127	-0.1000	5.23	202	335	0.947	34	252	-48.9	10	1.50	-0.27	-
15	-0.1968	-0.1201	1.50	186	295	0.881	32	231	-26.3	14	10.00	11.00	10.0
16	-0.2235	-0.1262	1.52	176	281	0.853	32	238	-26.4	16	10.00	6.00	5.00
17	-0.2100	-0.0974	2.60	177	271	0.745	30	243	-33.3	36	10.00	5.40	5.00
18	-0.2164	-0.1007	3.95	182	287	0.786	31	236	-35.3	5	15.00	11.40	10.00
19	-0.2109	-0.0986	3.51	196	350	0.876	30	254	-103.3	6	10.00	6.90	10.00
20	-0.2125	-0.0988	4.18	192	301	0.810	34	244	-36.4	8	10.00	12.90	10.00

[a] Minimum biological half-life [5].
[b] Estimated minimum initial dose (mg) [6-8].
[c] Calc.: Re-calculated values using Equation (1) utilizing linear coefficients in Table 3.
[d] Recommended initial dose.

Table 2. Molecular structure of 1,4-benzodiazepines [5].

Compound	Name	X1	X2	X3	X4
1	Bromazepam	H	H	Br	$HC_{15}X_4$=N
2	Cinolazepam	CH_2CN	OH	Cl	F
3	Clonazepam	H	H	NO_2	Cl
4	Clorazepate	H	COOH	H	H
5	Delorazepam	H	H	Cl	Cl
6	Diazepam	CH_3	H	Cl	H
7	Diclazepam	CH_3	H	Cl	Cl
8	Doxefazepam	CH_2CH_2OH	OH	Cl	F
9	Flubromazepam	H	H	Br	F
10	Fluarazepam	CH_2CH_2N (eth)$_2$H	Cl	F	-
11	Flutoprazepam cyclopropylmeth	H	Cl	F	-
12	Halazepam	CH_2CF_3	H	Cl	H
13	Lorazepam	H	OH	Cl	Cl
14	Lormetazepam	CH_3	OH	Cl	Cl
15	Nimetazepam	CH_3	H	NO_2	H
16	Nitrazepam	H	H	NO_2	H
17	Nordazepam	H	H	Cl	H
18	Oxazepam	H	OH	Cl	H
19	Phenazepam	H	H	Br	Cl
20	Temazepam	CH_3	OH	Cl	H

2. Method of calculations

All electronic structure calculations are based on Density Functional Theory [9]. The calculations exploit the BP86 functional and cc-pVDZ basis set. BP86 functional includes Becke's 88 exchange and Perdew's 86 correlations [10, 11]. cc-pVDZ basis set (correlation consistent polarized double zeta) was developed by Dunning [12]. The software used is Orca program [13]. Molecular volume was calculated as in the COSMO solvent scheme [14]. All parameters extracted from calculations were performed on an optimized geometry of the molecules.

We assumed that the minimum effective doses for human and the biological half-life of the different derivatives of benzodiazepines are related to some parameters extracted from the theoretical calculations. We select nine parameters satisfying the linear Equation (1).

$$\text{Dose} = a_0 + a_1 X_1 + a_2 X_2 \ldots\ldots\ldots\ldots + a_9 X_9 \quad (1)$$

where X_1 , X_2……X_9 are the nine selected parameters in the Equation (1). a_0, a_1, …., a_9 are the corresponding linear coefficients. The nine selected parameters for each compound are 1, HOMO energy in a.u. (HOMO); 2, LUMO energy in a.u. (LUMO); 3, Dipole moment in Debye (D); 4, Molecular volume in angstrom^3 (MV), 5, Molar mass in grams (MM); 6, The sum of positive charge over all atoms (CT); 7, Number of atoms in the molecule (NA); 8, Proton affinity at N1 (PA); and 9, Total energy in KeV (ET). The theoretically calculated parameters in addition to molar mass and number of atoms for the 20 derivatives are gathered in Table 1.

3. Results and discussion

The chosen 20 compounds are given in Table 2 and their structures are based on Figure 1. By applying linear least square regression analysis procedure to Equation (1), for different possible combinations of parameters, we found that the best fit achieved was with seven parameters out of nine which are LUMO energy, dipole moment, molecular volume, total positive charge, number of atoms, proton affinity and total energy. We notice that the HOMO energy and molar mass are missing. This indicates that the LUMO is more important than the HOMO in the linear fit. Also, the molecular volume is superior over the molar mass. The same procedure was applied using Equation (1), with the same nine parameters, but with $t_{1/2}$ as a dependent variable. Where $t_{1/2}$ is the biological half-life of the drug in the human body. In this case, we came to the conclusion that the same seven parameters are giving the best fit to Equation (1).

Table 3. Linear square regression coefficients of best fit. (R = Correlation coefficient).

Parameter	R	Error	a_0	HOMO	LUMO	D	MV	MM	CT	NA	PA	ET
Minimum dose	0.9359	2.70	41.25	0.0	-490.15	0.7537	0.8291	0.0	-140.50	0.6345	-0.6229	-0.1394
Biological half-life	0.8120	19.10	113.90	0.0	1335.00	-1.3420	-1.2170	0.0	165.10	4.4560	707.1	0.2932

Table 4. Energy gap between carboxylate and zwitterion form of clorazepate as in Figure 2.

Solvent	Dielectric constant	Refractive index	Gap (eV)
Hypothetical	200.00	1.330	0.20
H_2O	80.40	1.330	4.85
DMSO	47.20	1.479	5.07
CH_3OH	32.63	1.329	5.29
Acetone	20.70	1.359	5.71
$Cl\text{-}CH_2\text{-}CH_2\text{-}Cl$	10.36	1.445	6.68
$Cl\text{-}CH_2\text{-}Cl$	9.08	1.424	6.93
THF	7.25	1.407	∞
Gas phase	-	-	∞

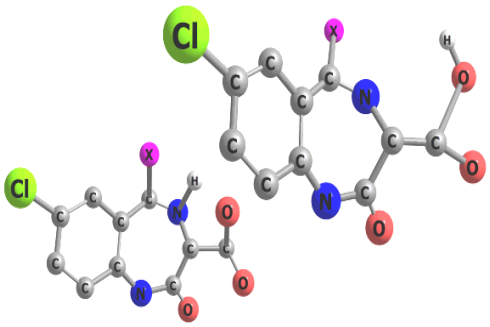

Figure 2. Different proton migrations of clorazepate molecule. X = Phenyl.

The linear coefficients of the Equation (1) with the best fit are given in Table 3 for minimum dose (first row) and for biological half-life (second row). The importance of each parameter in the fit is proportional to its numerical value. For example, the LUMO energy has more weight than the total charge and so on.

The importance of these coefficients is that, we can use them approximately to estimate the minimum dose or the biological half-life for a newly prepared derivative. On the other hand, we can find the contribution of each parameter in estimating the required properties. For example looking in Table 3, it is clear that the magnitude of the LUMO coefficient makes it the largest contributor to the minimum dose value. The negative sign of the coefficient indicates an inversely relation. Since the protein binding abilities of these benzodiazepines do not vary considerably among them [5], so that the values of calculated coefficients (Table 3) will be expected to be of little significance. The strength of pharmacological activities [15], which reflect the expected alteration of the magnitude of binding of benzodiazepines with GAMA-type A receptor. Accordingly, the minimum dose and smaller dose indicate a stronger binding. Also, it is connected to the biological half-life of the compound; larger half-life will indicate stronger binding affinity. From Table 3, we can decide which structure parameters having the larger effect on the magnitude of the binding strength between the benzodiazepines and the GABA-type A receptor.

As a first argument the strength of binding with GABA-type A receptor will be expected to be influenced by parameters like MV (related to the receptor cavity), dipole moment and CT assuming the receptor is polar. Also, LUMO energy assuming a possible electron transfer from the receptor to the LUMO empty level. For example, looking at Table 3, taking in your account the above discussion relating the minimum dose to the binding capacity with the receptor, it is obvious that as the molecular volume increases binding strength decreases and as the CT and LUMO energy increase the binding capacity increases.

We used the calculated linear coefficients to estimate back the expected doses of our compounds which are given in Table 2. Most of the calculated doses are close enough to the value of the original doses (minimum initial dose) extracted from literature [6-8]. Some of the doses are far from the values of the original doses and one of them has an unacceptable negative value. The latter value can be explained on the basis that the original value is rather small compared to the overall error of the calculations (~2.60) (Table 3). Since the original doses were unreliably estimated as best as random, we assume that our calculated values are close enough to hypothetical recommended values. The recommended values are based on both calculated and to some extent actual dose. These are given also in Table 1.

3.1. Clorazepate molecule

The clorazepate molecule (Figure 2) is an interesting case as it contains a carboxylate group and a free lone pair on neighboring N1 making the possibility for the proton of the carboxylate to migrate to N1 forming a zwitterion.

Since the latter is a strongly polar compound, we studied the calculated total energy of the two separated forms in different solvents using the COSMO model. The calculated energy gap [E_{total} (Zwitterion) – E_{total} (Carboxylate)], in different solvents, are given in Table 4.

Since the total energy has a negative value, a positive energy gap indicates that the carboxylate form of clorazepate molecule is the more stable, which is true for all cases. But the energy gap decreases as the dielectric constant increases and reaches a very small value (0.20 eV) for the very polar hypothetical solvent. We assumed that equilibrium between the two forms is established in solution. The equilibrium is more shifted to the zwitterion form as the dielectric constant increases. The ∞ gap (Table 4) means that the carboxylate form is the only possible form under any circumstances. This happens for solvents of low dielectric constants and for the gas phase.

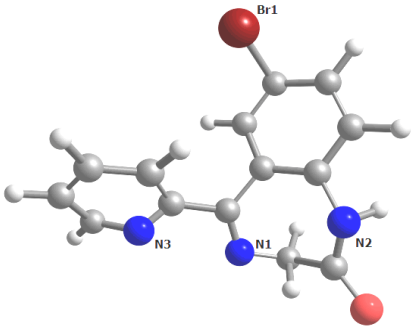

Figure 3. Structure of bromazepam molecule where N1 and N3 are located.

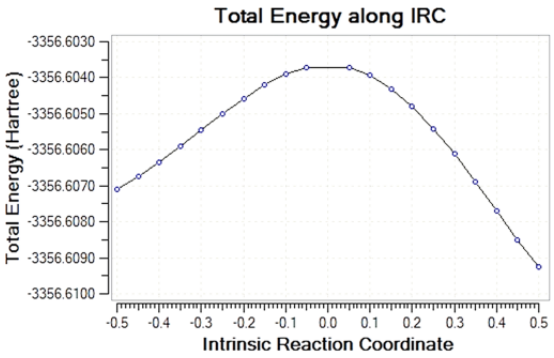

Figure 4. Reaction path of proton transfer between N1 and N3 in bromazepam ion.

3.2. Bromazepam molecule

The bromazepam molecule contains an extra aza nitrogen atom at position N3, due to the attachment of a pyridine molecule at C1 (Figure 3).

The protonated molecule has two possibilities, where the proton is attached to either N1 or N3. The $N1H^+$ form was found to be (by calculations) more stable than the $N3H^+$ form. Nevertheless a proton transfer is possible between the two forms making an intermediate transition state at certain point in the reaction path (Figure 4). The transition state energy is located at the maximum of the curve representing the reaction path.

The energy of the $N1H^+$ form is located at the right end of the curve. It is clear from the curve (Figure 4) that $N1H^+$ is the most stable form. The reaction path of curve in Figure 4 was calculated by a well-known procedure [16].

4. Conclusion

A scheme was proposed to find a correlation between the minimum effective dose of the different derivatives known as 1-4 benzodiazepines with certain theoretically calculated parameters. These parameters were calculated using quantum mechanics DFT approach. The correlation was found reasonable for some molecules. A special studies were devoted to two interesting molecules namely clorazepate and bromazepam. We discussed the proton transfer in both cases.

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Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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