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Scientific paper

COMPARISON OF TWO METHODS FOR THE ESTIMATION OF STABILITY OF COPPER(II) *BIS*-COMPLEXES WITH AROMATIC LIGANDS RELEVANT TO ALZHEIMER'S DISEASE

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In order to compare the density functional theory (DFT) and the method with the molecular valence connectivity index of the 3rd order ($^3\chi^v$) in the estimation of stability constants log β_2, we used copper(II) complexes with thioflavin-based intercalation compounds designed for application in Alzheimer's disease. Correlation of ten log β_2 values calculated by DFT with $^3\chi^v$ yielded r=0.988 and S.E.=0.85. The correlations of indices I_{NG}, HOMA and $^3\chi^v$ with log β_2, and the intercorrelations between the indices revealed the crucial influence of $^3\chi^v$ on the prediction of the stability of these complexes.

KEY WORDS: *aromaticity, density-functional theory (DFT), regression models, stability constants, topological indices*

Alzheimer's disease (AD), the leading mental disorder of the elderly population in developed countries, is closely related to copper metabolism (1). Next to the liver, the brain contains the second highest cellular concentration of copper, which is more frequent in grey matter (60 μmol L^{-1} to 110 μmol L^{-1}) than in white matter (25 μmol L^{-1} to 79 μmol L^{-1}) (2). Patients with AD have elevated copper(II) concentrations in whole blood (3). Even more importantly, copper(II) concentrations in the senile plaques of AD patients reach 400 μmol L^{-1}, which is nearly four times as much as usual grey matter content (2). These findings led George J. Brewer, Emeritus Professor at the Michigan Medical School, to the hypothesis that AD could be caused by copper(II) poisoning (4, 5). This hypothesis is further supported by the finding that this disease is still virtually unknown in developing countries, as was the case in developed countries 50 to 60 years ago. Professor Brewer found the principal reason for the epidemic of AD in elevated copper concentrations in drinking water caused by copper plumbing (6) and extensive red meat (especially beef) (7, 8) and multi-vitamin mineral pill consumption (9).

This hypothesis is also supported by research on the molecular level. The main mechanism in the development of AD is the formation of extracellular amyloid plaques in the brain. These plaques are composed of β-amyloid peptides (Aβ) (10), a normal cleavage product of the larger membrane amyloid precursor protein (APP) (11). Human Aβ binds copper, in contrast to rodent peptides (due to mutations Arg5 → Gly, Tyr10 → Phe, His13 → Arg). This serves as a very reasonable explanation for the virtual absence of Aβ deposits in normal rodent brains (12).

NMR (13) and AFM (14) studies have shown that copper(II) influences the aggregation behaviour of the Aβ peptide. The second, more vital, influence of

copper in the development of AD is the reduction of Cu^{2+} to Cu^{+} via the Aβ peptide. This process directly produces hydrogen peroxide (15) and, subsequently, reactive oxygen species (ROS) (16, 17). Copper(II) chelators, especially ligands capable of binding to the Aβ peptide, are therefore viewed as potential drugs and diagnostic tools for the treatment of AD (18, 19). Among these compounds is a class of ligands with a common core of the thioflavin T (ThT) and clioquinol (CQ) molecule (Figure 1). They were designed with the notion that they possess the lipophilicity adequate for crossing the blood-brain barrier as well as potential antioxidant properties. They also have a structure suitable for iodine substitution to the ligating group at the para position, which enables their use in diagnostics (20, 21).

After testing the $^{3}\chi^{v}$ index on various copper(II) (23), bivalent transition metal (24), and lanthanide complexes (25), but not yet on aromatic compound complexes, we found these copper(II) chelators suitable for testing and developing our method for the prediction of stability constants of coordination compounds based on the connectivity index $^{3}\chi^{v}$ (22). Unfortunately, among the ten complexes we studied, only two overall stability constants (β_2) were measured (20). Thus, we correlated the $^{3}\chi^{v}$ index to the stability constants ($\log \beta_2$) calculated by the density functional theory (DFT) (21). Also, we studied the referred correlations (21) of aromatic indices I_{NG} and HOMA (used to investigate the influence of Möbius metalloaromaticity (26, 27) on stability) *vs.* $\log \beta_2$, to compare their influence with that of the $^{3}\chi^{v}$ index.

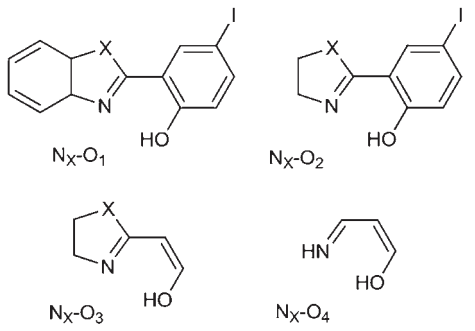


Figure 1 *Constitutional formulas of aromatic ligands; X is NH, O or S.*

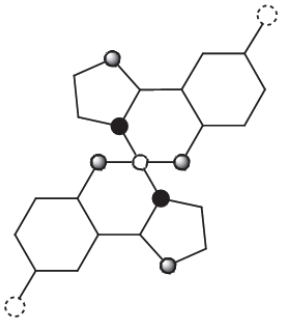


Figure 2 *Graph representation of [Cu(N_O-O2)$_2$]. Heteroatoms are marked with ○ (Cu), ● (N), ◘ (O), and ◌ (I).*

METHODS

Calculation of topological indices

The molecular valence connectivity index of the 3rd order $^{3}\chi^{v}$ was calculated using the E-DRAGON program system, developed by R. Todeschini and coworkers, which is capable of yielding 119 topological indices in a single run, along with many other molecular descriptors (28, 29). The connectivity matrices were constructed with the aid of the *Online SMILES Translator and Structure File Generator* (30).

The $^{3}\chi^{v}$ connectivity index (31-36) was defined as:

$$^{3}\chi^{v} = \sum_{path} [\delta(i)\,\delta(j)\,\delta(k)\,\delta(l)]^{-0.5} \quad (1)$$

where $\delta(i)$, $\delta(j)$, $\delta(k)$, and $\delta(l)$ are weights (valence values) of vertices (atoms) i, j, k, and l making up the path of length 3 (three consecutive chemical bonds) in a vertex-weighted molecular graph. The valence value, d(i), of the vertex i was defined by:

$$\delta(i) = [Z^{v}(i) - H(i)]/[Z(i) - Z^{v}(i) - 1] \quad (2)$$

where $Z^{v}(i)$ is the number of valence electrons belonging to the atom corresponding to vertex i, $Z(i)$ its atomic number, and $H(i)$ the number of hydrogen atoms attached to it. It should be stressed that $^{3}\chi^{v}$ is only a member of the family of valence connectivity indices $^{n}\chi^{v}$, which differ among each other by path length, *i.e.* the number of δ´s in the summation term (Equation 1).

The $^{3}\chi^{v}$ index for all *bis*-complexes was calculated from their graph representations assuming that the Cu(II) ion is tetracoordinated (Figure 2) (24).

Regression calculations

Regression calculations, including the leave-one-out procedure (LOO) of cross validation were done using the CROMRsel program (37). The standard error of the cross validation estimate was defined as:

$$S.E._{cv} = \sqrt{\sum_i \frac{\Delta X_i^2}{N}} \quad (3)$$

where ΔX and N denote cv residuals and the number of reference points, respectively.

RESULTS AND DISCUSSION

In order to compare the efficiency of the two methods for the estimation of stability constants, DFT and the $^3\chi^v$ index, we referred to log β_2 DFT values (21) (Table 1). Although the DFT values {15.1 and 11.0 for $[Cu(N_O\text{-}O1)_2]$ and $[Cu(N_S\text{-}O1)_2]$, respectively} were far from their experimental values (23.1 and 20.3), as obtained by UV-VIS spectrometry (20), the authors had, by mistake, stated that the agreement was remarkable (21). However, if we direct our attention to the relative values of log β_2s obtained by either DFT or spectrophotometry, it is evident that log β_2 $[Cu(N_O\text{-}O1)_2]$>log β_2 $[Cu(N_S\text{-}O1)_2]$ for both methods, being 4.1 and 2.8 for DFT and spectrophotometry, respectively.

Bearing all this in mind, we reproduced log β_2 (DFT) values through our method based on the $^3\chi^v$ index. Simple regression (Figure 3) yielded a correlation coefficient of r=0.988 and a standard error of cross-validation of $S.E._{cv}$=0.97 (Model 1, Table 2). Due to such a good correlation, we can deem our method equally successful as the DFT method, but much less demanding.

Table 1 *Logarithm of stability constants of copper(II)* bis-*complexes with 10 aromatic ligands, and values of their metalloaromaticity (I_{NG} and HOMA) and connectivity $^3\chi^v$ indices.*

No.	complex	log β_2[a]	log β_2[b]	I_{NG}[c]	HOMA[c]	$^3\chi^v$
1	$[Cu(N_{NH}\text{-}O1)_2]$	15.1	15.7	0.0174	0.658	11.753
2	$[Cu(N_{NH}\text{-}O2)_2]$	19.1	19.0	0.0167	0.545	9.701
3	$[Cu(N_{NH}\text{-}O3)_2]$	24.1	24.6	0.0183	0.848	6.412
4	$[Cu(N_O\text{-}O1)_2]$	15.1	16.4	0.0174	0.659	11.404
5	$[Cu(N_O\text{-}O2)_2]$	18.8	19.6	0.0172	0.641	9.406
6	$[Cu(N_O\text{-}O3)_2]$	24.7	25.0	0.0188	0.915	6.130
7	$[Cu(N_S\text{-}O1)_2]$	11.0	11.0	0.0170	0.555	14.504
8	$[Cu(N_S\text{-}O2)_2]$	16.1	14.9	0.0172	0.572	12.036
9	$[Cu(N_S\text{-}O3)_2]$	22.8	20.6	0.0188	0.894	8.637
10	$[Cu(N\text{-}O4)_2]$	30.8	30.9	0.0202	0.939	2.613

[a] DFT values from Ref. 21
[b] Cross-validated values (Model 1, Table 2)
[c] Ref. 21

Table 2 *Regression models for the estimation of the log* β_2 *of Cu(II)* bis-*complexes.*

model	descriptor	complexes	regression coefficients		r	S.E.	$S.E._{cv}$
			slope(S.E.)	intercept(S.E.)			
1	$^3\chi^v$	all	-1.667(91)	35.20(89)	0.988	0.85	0.97
2		1, 2, 3, 10	-1.693(46)	35.17(39)	0.999	0.23	0.40
3		4, 5, 6, 10	-1.785(17)	35.54(14)	0.999	0.08	0.21
4		7, 8, 9, 10	-1.65(13)	35.8(14)	0.994	0.84	2.44
5	I_{NG}	all	4711(897)	-65(16)	0.880	2.64	3.24
6		1, 2, 3, 10	4025(1372)	-51(25)	0.901	2.55	4.50
7		4, 5, 6, 10	4736(974)	-65(18)	0.960	1.67	3.06
8		7, 8, 9, 10	5608(768)	-82(14)	0.982	1.41	2.63
9	HOMA	all	31.9(66)	-3.3(49)	0.863	2.81	3.66
10		1, 2, 3, 10	32(14)	-1(11)	0.854	3.05	7.01
11		4, 5, 6, 10	39(12)	-8.6(98)	0.915	2.40	4.84
12		7, 8, 9, 10	39(11)	-8.7(83)	0.931	2.72	5.45

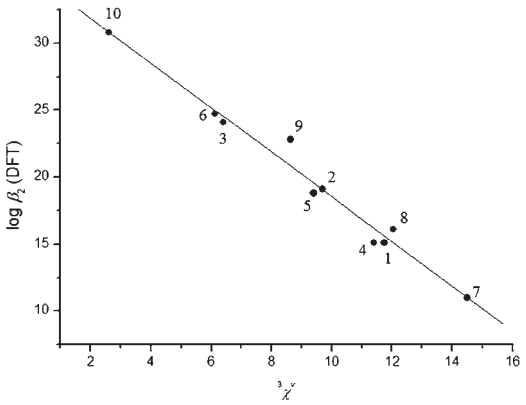
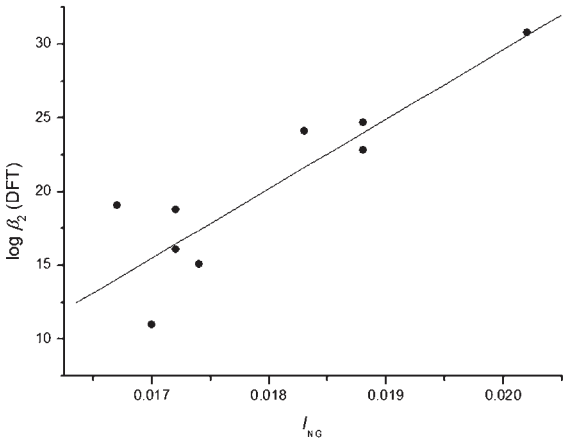
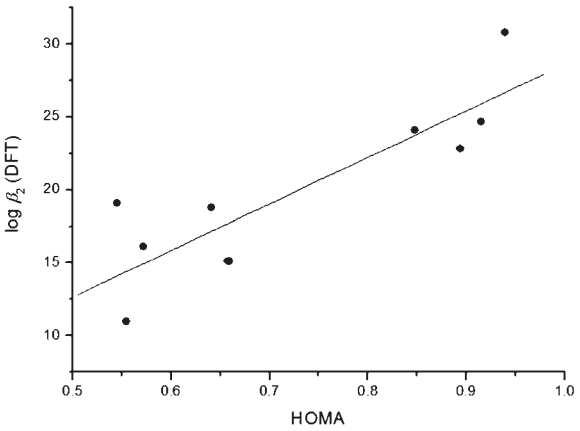


Figure 3 *Dependence of stability constant log* β_2 *(DFT) on the* $^3\chi^v$ *index for Cu(II)* bis-*complexes with ten aromatic ligands (Table 1, Model 1 in Table 2).*



a)



b)

Figure 4 *Dependence of stability constant log* β_2 *(DFT), of Cu(II)* bis-*complexes with ten aromatic ligands, on a)* I_{NG} *index (Model 5, Table 2) and b) HOMA index (Model 9, Table 2).*

We also analysed reported correlations (24) of indices defining metalloaromaticity, I_{NG}, and HOMA *vs.* log β_2 (Models 6-8, 10-12, Table 2), on three subsets, imida-complexes (1-3 and 10), oxa-complexes (4-6 and 10), and thia-complexes (7-10). Although the stability was positively correlated with I_{NG} and HOMA for all three subsets, the differences in log β_2 between complexes 1 and 2 and 4 and 5 showed an opposite trend. From the comparison of these correlations (Models 6-8, 10-12, Table 2) with the correlations obtained with the $^3\chi^v$ index (Models 2-4, Table 2), it is clear that $^3\chi^v$ is a substantially better index for modelling the stability of the studied complexes than I_{NG} and HOMA. Specifically, standard errors for $^3\chi^v$ regressions are an order of magnitude smaller than the standard errors of the regressions with other two indices, with the exception of the thia-complexes subset [7-10, Table 1); S.E.($^3\chi^v$):S.E.(I_{NG})=1:1.68 and S.E.$_{cv}$($^3\chi^v$):S.E.$_{cv}$(I_{NG})=1:1.08 (for HOMA the ratios are 1:3.24 and 1:2.23)]. Accordingly, the regression of $^3\chi^v$ to log β_2 on all complexes (Model 1, Table 2, Figure 3), yielded much better results than the regression with metalloaromaticity indices I_{NG} and HOMA (Models 5 and 9, Table 2, Figure 4).

Bivariate linear regressions of I_{NG} and $^3\chi^v$ *vs.* log β_2 (r=0.990, S.E.=0.77, S.E.$_{cv}$=1.11) and HOMA and $^3\chi^v$ *vs.* log β_2 (r=0.990, S.E.=0.79, S.E.$_{cv}$=1.19), did not yield improvement over univariate regression with $^3\chi^v$. To the contrary, S.E.$_{cv}$ rose from 0.97 to 1.11 and 1.19, respectively. In addition, the intercorrelations between $^3\chi^v$ and indices I_{NG} and HOMA (Figure 5) show that the better the correlation of I_{NG} and HOMA to $^3\chi^v$, the better the correlation of I_{NG} and HOMA to log β_2 (Models 6-8, 10-12 in Table 2). All of the

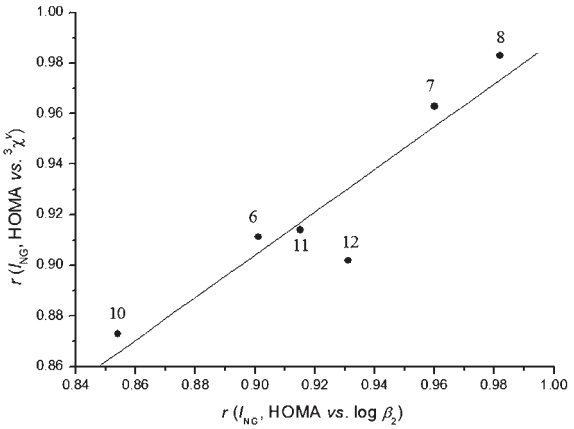


Figure 5 *The correlation coefficient of* I_{NG} *and HOMA to* $^3\chi^v$ vs. *the correlation coefficient of* I_{NG} *and HOMA to log* β_2 *(Models 6-8, 10-12 in Table 2).*

aforementioned strongly suggests that the information needed for stability modelling of the studied complexes stems almost exclusively from $^3\chi^v$.

CONCLUSION

We correlated the $^3\chi^v$ index to the stability constant log β_2 calculated by the density functional theory (DFT). Assuming that DFT log β_2's were fairly well correlated with experimental stability constants, we concluded that the method with $^3\chi^v$ was equally good but far simpler for the estimation of stability constants in comparison to the DFT method. As DFT also proved unable to estimate the absolute log β_2 values (21), it could not be ascertained, at least in our case, that DFT had any advantage over our method.

We also showed that $^3\chi^v$ correlates to the log β_2 of the studied complexes much better than metalloaromaticity indices I_{NG} and HOMA. Moreover, adding indices I_{NG} or HOMA into regression along with $^3\chi^v$ worsened the estimates. This indicates that $^3\chi^v$ encompasses structural information relevant to stability, including metalloaromaticity.

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Sažetak

USPOREDBA DVIJU METODA ZA PROCJENU STABILNOSTI *BIS*-KOMPLEKSA BAKRA(II) S AROMATSKIM LIGANDIMA RELEVANTNIMA ZA ALZHEIMEROVU BOLEST

Izabrali smo komplekse bakra(II) s interkalacijskim spojevima temeljenima na tioflavinu, koji su namijenjeni za liječenje Alzheimerove bolesti, kako bismo usporedili teoriju funkcionala gustoće (DFT) s metodom molekularnog valencijskog indeksa 3. reda ($^3\chi^v$) za procjenu vrijednosti konstanti stabilnosti log β_2. Korelacija deset vrijednosti log β_2 izračunatih metodom DFT s $^3\chi^v$ indeksom dala je r=0,988 i S.E.=0,85. Korelacije indeksa I_{NG}, HOMA i $^3\chi^v$ s vrijednostima log β_2 te međukorelacije indeksa pokazuju bitan utjecaj $^3\chi^v$ na predviđanje stabilnosti istraživanih kompleksa.

KLJUČNE RIJEČI: *aromatičnost, konstante stabilnosti, regresijski modeli, teorija DFT, topološki indeksi*

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