communications in mathematical
match
and in computer chemistry

no. 44, October 2001
MATCDY (44) 297 - 304 (2001)
ISSN 0340 - 6253

QUANTITATIVE ESTIMATION OF ELECTROSTATIC COMPLEMENTARITY*

Gábor Náray-Szabó

Department of Theoretical Chemistry, Loránd Eötvös University, H-1117 Budapest, Pázmány Péter st. 1A, Hungary

Abstract. A quantitative measure of electrostatic host-guest complementarity, as defined by Umeyama and co-workers and slightly modified by us, is used to characterise the packing of sulphur-containing macrocycles in a crystalline environment. Molecular graphics studies and a semi-quantitative analysis indicate that, at least partly, electrostatic stabilisation emerging from complementarity accounts for the formation of relatively energy rich structures in the crystal. The better is the complementarity with the crystalline environment the higher is the energy of a ring in the solid state as compared to the absolute minimum in the gas phase. A further interesting case of complementarity is the electrostatic fit between enzyme active sites and their protein environment. The (- + -) charge pattern, characterising the active sites of a number of hydrolytic enzymes, is stabilised by the electrostatic pattern provided by the surrounding protein. It was found that the measure of the electrostatic complementarity between the active site and the environment correlates well with the experimentally determined activities. On this basis we propose to use this measure for the characterisation of enzyme catalytic power.

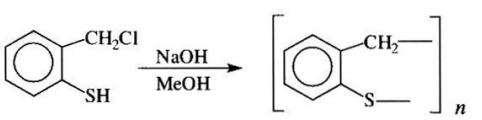
INTRODUCTION

Host-guest complementarity is one of the key determinants protein-ligand interactions, host-guest complexation, crystal packing and nucleation (1-3). Complementarity has at least three aspects, steric, electrostatic and hydrophobic (4-6). Steric fit means that interacting atoms of host and guest avoid steric conflicts and, simultaneously, crevices should be filled as densely as possible reducing the free space between interacting atoms to a minimum. Electrostatic fit requires the maximum ionic and polar (e.g. hydrogen-bonding) interaction

* Dedicated to Prof. A. Balaban on the occasion of his 70th birthday.

between partners, while hydrophobic complementarity corresponds to the association trend between non-polar groups in aqueous medium. While the steric factor is quite often emphasised when discussing host-guest complexation, electrostatic and hydrophobic determinants of complementarity are less frequently treated.

In this paper we discuss two specific examples of electrostatic complementarity on the basis of a quantitative measure defined by Umeyama et. al. (7). One refers to the crystal packing of sulphur containing macrocycles where electrostatic effects by the environment stabilise energy-rich forms of the rings. These compounds, **1-5**, can be obtained by oligomerisation of 2-chloromethyl benzenethiol in the presence of sodium hydroxide and methanol (cf. Scheme) (8-10). Crystal structure of **3** has been determined by Kálmán et al. (11), others in our laboratory (12). The second example concerns the Asp...His...Ser catalytic



1: $n = 2$
2: $n = 3$
3: $n = 4$
4: $n = 5$
5: $n = 6$

Scheme

triad at the active site of serine proteases. We found that the protein and substrate electrostatic potentials, calculated on the van der Waals envelope of the triad, complement each other. Activities of five serine proteases for the same substrate correlate well with the measure of electrostatic complementarity.

MODELS AND METHODS

For the sulphur macrocycles we constructed crystal models using the SYBYL software (13) on the basis of the available X-ray structures (11,12). We considered the neighbours of the central molecule lying within a 500 pm radius and built up the whole cluster such a way that it reflects the overall crystal symmetry. Thus, the environment of the central molecule contains 14 to 20 neighbours depending on the position of the central molecule inside the asymmetric unit.

Three-dimensional structures of the enzymes treated were taken from the Protein Data Bank (14). We calculated the molecular electrostatic potential (MEP) for the crystal model with the semiempirical AM1 molecular orbital method as implemented in the MOPAC software (15,16), while for the catalytic triad formed by the aspartate, histidine and serine side chains of the active site as well as its environment with the DelPhi method (17) applying net charges for the atoms of the catalytic triad from semiempirical calculations (15). This is a fair model of the transition state as shown by Asbóth and Polgár (18). In order to construct a model of the enzyme-substrate complex we optimised the structures with molecular mechanics and molecular dynamics as implemented in the SYBYL software (13). For further details see Ref. 19.

For the calculation of electrostatic complementarity in point i we used the formula proposed by Umeyama et al. (7)

$$P_i = \text{sign}(V_i^H \times V_i^G)(V_i^H \times V_i^G)^{1/2} \quad (1)$$

where V_i^H and V_i^G denote the molecular electrostatic potential in point i emerging from the host (crystal or protein environment) and guest (central molecule or catalytic triad), respectively. Electrostatic complementarity between a molecule and its environment is defined as an average for the set of N points, $\{i\}$, on the van der Waals surface

$$P = \Sigma P_i/N \quad (2)$$

Complementarity is the better, the more negative is P, corresponding to a larger value of the electrostatic interaction energy between associating partners. We considered only those points in eq. (2) which belong to regions near potentially hydrogen-bonding atoms (N, O, S, as well as attached hydrogen atoms) and electron-rich groups (phenyl ring), providing the major part of information inherent in the MEP.

Conformational analyses were done using a Monte Carlo (MC) based algorithm (20). Calculation of the energy content of ring conformations present in the crystal were calculated using the experimental structure as a starting point. In order to optimise the inaccurate hydrogen atom positions as obtained by X-ray diffraction, as well as to release eventual close contacts, we relaxed the structures without significantly deforming the original ring

conformation which was achieved by performing 10 minimisation steps using the steepest descent method. For further details see Ref. 12.

RESULTS AND DISCUSSION

Earlier we pointed out that crystal packing is influenced by electrostatic complementarity (21). If comparing all macrocycles studied it is found that with increasing ring size the deformation energy of a certain molecular conformation in the crystal, ΔE, also increases (cf. Table 1). Furthermore, the stronger is the complementarity with the environment (P that is proportional to the electrostatic interaction energy) the higher is the ring distortion energy with reference to the unperturbed, gas-phase conformation. We suppose that ring distortion is mainly due to the electrostatic component of packing effects. Our rule is clearly not obeyed by the dimer, **1**, which is almost completely rigid, thus cannot be deformed by crystal field effects at all. Applying regression analysis we obtain a rough linear proportionality between distortion energies and P with a correlation coefficient of 0.846 (cf. Figure 1).

TABLE 1 Quantitative measure of electrostatic complementarity (P in kJ/mol) for the packing of crystals of sulphur macrocycles *vs.* energy differences (ΔE in kJ/mol) between lowest energy gas-phase and actual crystal conformers. The nine different conformations of **4** are denoted by Arabic numbers from 1 to 9.

molecule		P	E		ΔE
			X-ray	minimised	
1		-10.6	78	75	3
2		2.9	95	85	10
		-11.7	160	126	34
4	1	-13.9	159	105	54
		-14.6	159	105	54
	3	-15.5	156.5	105	51.5
	4	-15.6	159	105	54
	5	-15.6	156.5	105	51.5
	6	-15.9	159	105	54
	7	-17.4	159	105	54
	8	-18.8	159	105	54
	9	-19.3	156.5	105	51.5
5		-14.4	210	140	70

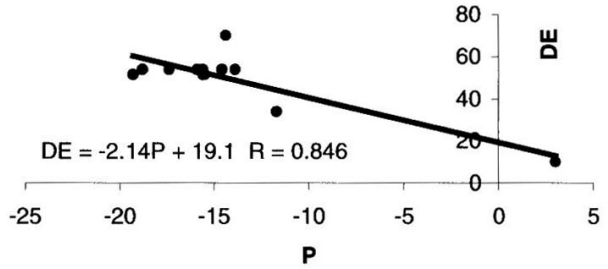


FIGURE 1. Proportionality between electrostatic complementarities (P) and ring distortion energies (DE) of sulphur macrocycles. Both quantities are in kJ/mol.

In other words this means that the energy gain due to electrostatic complementarity compensates the energy loss due to conformational distortion.

Experimental ligand-binding energies for five serine proteases with an identical substrate (succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide) are plotted *vs.* electrostatic complementarities on Figure 2.

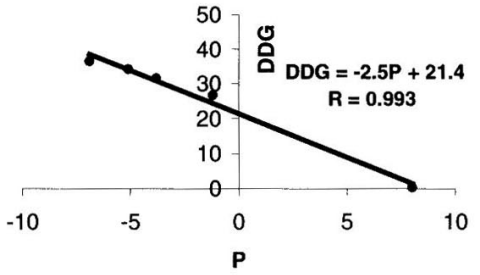


FIGURE 2. Proportionality between electrostatic complementarities (P) and experimental ligand-binding energies (DDG, *cf.* refs. 22-24) for five serine proteases with an identical substrate. Both quantities are in kJ/mol

The same type of linear correlation can be observed as in case of sulphur macrocycles, even the regression coefficients (2.14 and 2.5) as well as intercepts (19.1 and 21.4) are close to each other This indicates that the proportionality between electrostatic energies and complementarity values remains valid for two quite different cases. Both regression equations work for positive P values, too, indicating poor electrostatic fit between the macrocycle or the active site and the environment.

An important feature of electrostatic complementarity, as defined in eqs. (1-2) is that it reflects steric aspects of the electrostatic fit between host and guest. Attractive and repulsive regions of the interacting partners can be visualised by molecular graphics which adds an extra dimension to the analysis of interaction energies and optimal geometric arrangements.

CONCLUSIONS

We presented two examples for the quantitative description of electrostatic complementarity. The empirical relation of Nakamura et al. (7) using the product of host and guest electrostatic potentials seems to be appropriate for the estimation of relative magnitudes of binding energies even if it has no direct physical meaning. A precise definition of the electrostatic lock-and-key model should be based on the complementarity of the charge distribution of the guest and electrostatic potential of the host (25). Analysis of steric aspects of the fit via inspection of the electrostatic potential maps allows to draw conclusions that could not be not possible using mere numbers, measuring the interaction energy.

ACKNOWLEDGEMENT

This work was supported by grants from OTKA (National Fund for Scientific Research, Hungary) #T022191 and FKFP (Research and Development Fund for Higher Education) #0169/2000.

REFERENCES AND NOTES

[1] J.P. Behr, Ed., *The Lock and Key Principle. The State of the Art - 100 Years On*, Wiley, Chichester, 1994.

[2] G. Weber, *Protein Interactions,* Chapman and Hall, New York, 1992.

[3] A.I. Kitaigorodskii, *Molecular Crystals and Molecules,* Academic Press, New York, 1973.

[4] G. Náray-Szabó, *J. Mol. Graphics* **1989,** *7,* 76-81.

[5] G. Náray-Szabó, *J. Mol. Recogn.* **1994,** *6,* 205-210.

[6] G. Náray-Szabó and G.G. Ferenczy, *Chem. Rev.* **1995,** *95,* 829-847.

[7] H. Nakamura, K. Komatsu, S. Nakagawa, and H. Umeyama, *J. Mol. Graphics* **1985,** *3,* 2-11.

[8] W.D. Ollis, J.F. Stoddard, and M. Nógrádi, *Angew. Chem. Int. Ed. Engl.* **1975,** *14,* 168-175.

[9] D.J. Brickwood, W.D. Ollis, J.S. Stephanatou, and J.F. Stoddard, *J. Chem. Soc. Perkin Trans 1,* **1978,** 1398-1414.

[10] W.D. Ollis, J.S. Stephanatou, J.F. Stoddard, and M. Nógrádi, *J. Chem. Soc. Perkin Trans 1,* **1978,** 1421-1428.

[11] L. Párkányi, A. Kálmán, and M. Nógrádi, *Acta Cryst.* **1975,** *B31,* 2716-2720.

[12] Z. Böcskei, M. Fuxreiter, V. Harmat, L. Häming, G.M. Keserű, B. Marten, G. Náray-Szabó, T. Nusser, and G.M. Sheldrick, in preparation.

[13] *SYBYL* Version 6.0a, TRIPOS Associates, St. Louis, MO, 1993.

[14] H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, and P.E. Bourne, *Nucl. Acids Res.* **2000,** *28,* 235-242.

[15] J.J.P. Stewart, *QCPE Bull.* **1989,** *9,* 10-12.

[16] MOPAC Version 5.5, Quantum Chemistry Program Exchange 455, Indiana University, Bloomington, IN, 1989

[17] I. Klapper, R. Hagstrom, R. Fine, K. Sharp, and B. Honig, *Proteins* **1986,** *1,* 47-57.

[18] B. Asbóth and L. Polgár, *Biochemistry* **1983,** *22,* 117-123.

[19] T. Gérczei, B. Asbóth, and G. Náray-Szabó, *J. Chem. Inf. Comput. Sci.* **1999,** *39,* 310 315.

[20] I. Kolossváry and W.C. Guida, *J. Am. Chem. Soc.* **1996,** *118,* 5011-5019; MacroModel, Version 6.0, Department of Chemistry, Columbia University, New York, NY 10027, USA.

[21] P.P. Korkas, E. Weber, M. Czugler, and G. Náray-Szabó, *J. Chem. Soc. Chem. Commun.* **1995,** 2229-2230.

[22] N.A. Stambolieva, I.P. Ivanov, and V.M. Yomtova, *Arch. Biochem. Biophys.* **1992,** *194,* 703-710.

[23] R. Bone, A. Fujishinge, C.A. Kettner, and D.A. Agard, *Biochemistry* **1991,** *30,* 10388-10398.

[24] I. Venekei, L. Gráf, and W.J. Rutter, *FEBS Lett.* **1996,** *379,* 139-145.

[25] J. Grembecka, P. Kędzierski, W.A. Sokalski, and J. Leszczyński, *Phys. Chem. Chem. Phys.*, submitted.