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Evidences for "molecular volume fitting" concept in crystal growing from water solutions

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ABSTRACT

The fast methods for calculation of molecular volume and polar surface area are helpful for the selection of compounds with similar values of these descriptors. The selected molecules were used for growing crystals from water solutions by slow evaporation in room temperature method. The presented examples of effective crystallization support "volume fitting" concept.

Keywords: Molecular volume, polar surface area, crystallization, acid-base molecular-ionic complexes

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INTRODUCTION

The concept of molecular "volume fitting" arises from the observations of shape and structure of individual molecules of acids and bases [1]. In the simple and intuitive approach such cursory look leads to classification of molecules according to their size and polar surface area. To illustrate this concept one can consider some examples of molecules with small molecular volume (acids like formic, glyoxalic, sulfaminic or aminomethanesulfonic; bases like hydrazine, urea, guanidine or triazole) and large molecular volume (acids eg. egtazic, EDTA, 2-amino-1,5-naphthalenedisulfonic or mellitic; bases *eg.* tri-pyridyl-s-triazine, Reichardt's dye, tetraacetylenediamine or dinitrotyrosine). Similar classification includes molecules with small polar surface (acids *eg.* dimethylphenol, formic acid, methylphenol; bases *eg.* diethylmethylamine, tripropylamine, diazabicyclooctane or triethylamine), and large polar surface (acids *eg.* mellitic, egtazic, 3-amino-4-hydroxy-5-nitrobenzenesulfonic or picric; bases *eg.* melamine, arginine, biuret or asparagine).

As for non-polar molecules in most cases the chemical reaction takes place accidentally, while for polar molecules electrostatic dipole interactions increase the number of situations in which the reorganization of atoms and charges between reacting agents is possible. Therefore the conclusion arises that size of molecule (its volume) and polar surface play the important role. Where can we find the values of these parameters? Some traditional methods of calculations exist with different methodologies for generating 3-D structures (CORINA, CONCORD, geometry optimization, conformational sampling) [2] and for surface determination (Van der Waals, Conolly, Lee-Richards). These calculations are long lasting and specialized software is required to generate 3D molecular structures and to determine the surface itself.

A good practical solution is to use fast methods for calculation of volume and polar surface area [3, 4]). According to Ertl *et al.* [4], the calculation of topological polar surface area (TPSA) is based on the summation of tabulated surface contributions of polar fragments. These contributions were determined by least-squares fitting to the polar surfaces calculated using traditional methods for a large set of molecules. World Drug

Index was used (Derwent World Drug Index) for structure searchable database of drugs or active compounds. Available quarterly as in-house database for various software; http://thomsonreuters.com/products_services/science/science_products/a-z/world_drug_index/).

The molecules with apparent valence errors were removed, as well as molecules with molecular weights out of the 100-800 interval, and also those not having at least one oxygen, nitrogen, sulfur or phosphorus atom. Such pre-processed set contained approximately 35000 compounds. 43 types of fragments were differentiated. A criterion for belonging to particular type was the way in which the atom is connected to the rest of the molecule (bonding pattern).

The contributions of nitrogen atom in nitro group, nitriles, azides, ring nitrogen atom are different in bond patterns. Except polar fragments containing O and N, the slightly polar' fragments containing P and S were also included in calculations. Furthermore, the contributions of particular fragments should be re-evaluated according to the strength of hydrogen bonds they can form. This suggestion is crucial especially in the case of acid-base molecular-ionic complexes when intense hydrogen bond networks are formed in crystal structure.

MATERIALS AND METHODS

The starting compounds: melamine, Aldrich, 99%, L-asparagine, Sigma, ≥98% (TLC), L-lysine, Aldrich, 99%, 2-methyl-5-nitroaniline, Aldrich, 99%, 2-methyl-4-nitroaniline, Aldrich, 97%, 2-amino-5-nitropyridine, Fluka, technical, ≥95% (NT), 2-amino-4-methyl-3-nitropyridine, Fluka, purum, ≥97% (NT), 2-amino-4-methyl-5-nitropyridine, Aldrich, 98%, 2-hydroxy-6-methyl-5-nitropyridine, Aldrich, 97%, L-phenylalanine, Sigma-Aldrich, reagent grade, ≥98%, piperazine, Aldrich, 99%, N-acetylglycine, Aldrich, 99%, aniline, Aldrich, 99%, 2-aminopyridine, Aldrich, 99%, L-tartaric acid, Aldrich, 99%, picric acid, Sigma-Aldrich, reagent grade, 98%, trichloroisocyanuric acid, Aldrich, 97%, 4-hydroxybenzenesulfonic acid, FERAK LABORAT GMBH BERLIN, pure, adipic acid, Aldrich, 99%, 4,5-dichlorophthalic acid, Fluka, purum, ≥97% (T), malonic acid, Fluka, purum, ≥98% (T) and fumaric acid, Aldrich, 99% were used as purchased. The compounds were dissolved in doubly distilled water in the stoichiometric ratio. Solutions were purified with the aid of active charcoal and slowly evaporated at room temperature.

RESULTS AND DISCUSSION

The fast methods for calculation of molecular properties described in Introduction were implemented by Molinspiration and are available as a free on-line tool for internet cheminformatics community (http://www.molinspiration.com). Additionally, this program - written in Java - allows one to use SMILES - convenient chemical nomenclature [5] that accelerates the calculations significantly. Using this very convenient and practical tool the volumes and polar surfaces for 309 molecules were calculated (126 acids and 183 bases). Additionally the sums of Van der Waals spheres were taken into account. The obtained results covered the range of 251-5168 [$Å^3$×100] for molecular volume, 0-22380 [$Å^2$×100] for polar surface area and 419-25871 [$Å^3$×100/(4/3π)] for sum of Van der Waals spheres.

Water solutions of different acids and bases were prepared for the compounds having the molecular volume and polar surface area as close as possible. For chosen molecules the values of considered parameters are collected in Table 1.

Table 1: Comparison of numerical values of sum of the Van der Waals spheres, molecular volume and polar surface area for molecules present in the prepared solutions

Compounds forming crystalline complex	sum of the Van der Waals spheres [$Å^3$×100/(4/3π)]	molecular volume [$Å^3$×100]	TPSA (polar surface area) [$Å^2$×100]	Reference
melamine	4743	1054	11675	[6, 7]
L-tartaric acid	5108	1163	11506	
L-asparagine	5145	1148	10600	[7, 8]
picric acid	7056	1621	15770	
L-lysine	6814	1462	8934	this work
trichloroisocyanuric acid	5391	1377	6601	
2-methyl-5-nitroaniline	6267	1352	6920	this work
4-toluenesulfonic acid	6021	1315	7460	
2-methyl-4-nitroaniline	6267	1352	6920	this work
4-hydroxybenzenesulfonic acid	6021	1315	7460	
2-amino-5-nitropyridine	5138	1145	8474	[9]
4-hydroxybenzenesulfonic acid	6021	1315	7460	
2-amino-4-methyl-3-nitropyridine	5975	1312	8210	this work
4-hydroxybenzenesulfonic acid	6021	1315	7460	
2-amino-4-methyl-5-nitropyridine	5975	1312	8210	this work
4-hydroxybenzenesulfonic acid	6021	1315	7460	
2-hydroxy-6-methyl-5-nitropyridine	5781	1278	7894	this work
4-hydroxybenzenesulfonic acid	6021	1315	7460	
L-phenylalanine	7396	1560	6332	this work
4,5-dichlorophthalic acid	7190	1651	7460	
piperazine	4438	938	2406	[10]
4-hydroxybenzenesulfonic acid	6021	1315	7460	
melamine	4743	1054	11675	this work
N-acetylglycine	4600	1044	6640	
aniline	4529	953	2602	this work
malonic acid	3569	834	7460	
2-aminopyridine fumaric acid	4237	912	3892	[11]

The fact that crystals are formed after pairing acids and bases by similar (matched) volume and polar surface area is not trivial taking into account the time needed for growing big crystal. It is not claimed that these geometrical features are essential for crystallization itself. Unmatched compounds crystallize also; however, the crystallization of matched compounds proceeds faster and more efficiently in contrary to the case when unmatched compounds are used. Very probable the condition of similar volume only is sufficient to obtain large single crystals quickly.

CONCLUSION

"Similar likes similar". This rule applying to molecules of both acids and bases can explain the results presented in this work. The probability to persist enough time in preferable orientation and to "catch" each other by appropriate functional groups is significantly greater if the sizes of reacting molecules are similar. Such a conclusion is experimentally supported by the fact that apart from several exceptions, the best crystalline complexes were obtained choosing the chemical compounds (acids and bases) whose molecules had similar size (volume) and similar polar surface. Such approach allows accelerating the process of obtaining good quality material for further studies (dielectric, nonlinear optical, polarised vibrational *etc*). It is commonly known that in the case of materials with interesting physical and chemical properties the possession of single crystals of sufficient size is the conditio sine qua non for performing even the routine measurements.

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