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From crystallographic data to the creation of a binding model with a receptor

J. Karolak-Wojciechowska

Institute of General and Ecological Chemistry, Technical University, 90-924, Lodz Zwirki 36, Poland

Abstract

The basic model for glycine receptor site has been proposed based on the ligands incorporated spatially inflexible main skeleton. The search for compounds, which are selectively bound to the receptor, is now based on topological and/or stereochemical requirements and restrictions derived for the glycine binding site. IsoStar is the definitive database of experimental and theoretical information on non-bonded interactions. It has been designed to play a prominent role in the field of rational drug design. We applied IsoStar in our search for the model of glycine binding site of the NMDA receptor. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: IsoStar; Glycine receptor ligands; Arylidene-imidazolone-glycines

Various techniques, such as spectroscopic and diffraction methods, can reveal information on molecular structure. However, crystal structure analysis appears to be the most efficient method for elucidating the three-dimensional (3-D) structures of the molecules. During the last three decades the number of solved structures has grown rapidly. All crystallographic information is available in the electronic database form, and the most popular are CSD (Cambridge Structures Data Base) and the Brookhaven Protein Data Bank (PDB).

The required precise information concerning a molecule is provided by the crystal structure analysis. Yet, all obtained data usually describe only one conformation from a number of possible structures. Nevertheless, a thorough investigation reveals that one can draw a variety of conclusions regarding the dynamic behavior, flexibility, and reactivity of molecules from crystal structure analysis. However, the question remains: how to extract this information from the enormous pool of crystal structures from only one conformation of a molecule? The first method involves the comparative analysis of available, e.g. from CSD, structures of a number of closely related crystals, molecules, or their fragments and the determination of their differences. The second method is not only restricted to crystallographic information. It assumes that crystallographic 3-D data form the starting point for conformational analysis by calculations.

In this study, the first method was used — the crystal data correlation method. The application of this method became possible thanks to the new program, called IsoStar, incorporated into the CSD database. We would like to present the very first, partially published already, example of IsoStar application. It can be used for refinement of structure details of the binding site of the receptor. One of the binding sites of the NMDA receptor, namely glycine binding site, was chosen for this investigation.

The basic model for glycine receptor site (Fig. 1a) has been proposed based on ligands that incorporate spatially inflexible main skeleton [1]. At the same time, we have studied a series of arylidene-imidazolone glycines (acids, esters and amides) with confirmed affinity to the NMDA receptor and with incorporated moiety characterised by rotational freedom [2]. Topological fitting of the glycine binding site comprises a size-limited hydrophobic pocket, hydrogen bond acceptors and donors (obligatory NH groups), and a coulombic attractive region (carboxylic group). This model may be easily adapted to arylidene-imidazolone glycines, as shown in Fig. 1b.

The data obtained from IsoStar [3] were used to validate the proposed model. These data describe the spatial distribution of non-bonded contacts between selected groupings — the 'central group' and the 'contact group'. In this example, we have found surfaces of

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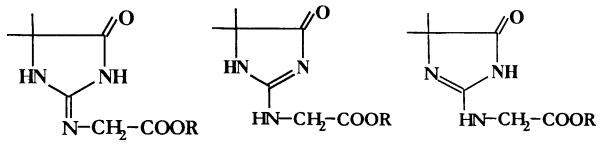
crystallographically registered interactions for seven groups existing in the presented model. From these 'puzzles' of phenyl, charged acid, ester, amide, carbonyl, sp-nitrogen from aromatic heterocycles and acyclic N–H groups, we composed the artifact of binding site with measurable dimensions of individual regions.

It was documented that affinity to the receptor of imidazolono-glycine derivatives depends mainly on the negative charge of the carboxylic group residue. Every substitution lowering this charge (and blocking ionisation) limits contact with other chemical objects. These differences are clearly visualised by scattegrams, which summarise crystallographically confirmed areas of non-bonded contacts for COO^-, COOR and $CONH_2$ groups with H–X (X = O, N) (Fig. 2). Areas of contact are explicitly different.

All imidazolone-glycines may exist in at least three tautomeric forms, but hydrogen at glycine nitrogen (**b** and **c**) is essential for affinity to the glycine receptor.



a b c

However, it seems to be difficult to form N(from glycine)–H···A bonds in close spatial proximity of endocyclic nitrogen with sp hybridisation (**c** form). Therefore, the formation of two N–H···A bonds (by form **b**) seems to be preferred. It should be emphasised that such H bond patterns are observed in the structure of corresponding ester solved by us with two nitrogen atoms anchored via H bonds to the common acceptor. Surfaces of crystallographically registered interactions for corresponding H bond acceptors and donors are given in Fig. 3.

All the molecules of the screened arylidene-imidazolones (after energy minimisation at AM1 approximation) exhibit *Z* configuration with two rings in main moiety. This moiety can easily simulate the kyrturenic acid skeleton with arylidene fragment located in the lipophilic pocket (Fig. 1b). The data from IsoStar indicate that surfaces fit for π···H–C interactions are located above and below the phenyl ring (Fig. 4).

As was explained by the above given example, the IsoStar program enables one to obtain crystallographic data, which may reveal information on the geometry, energies, and frequencies of occurrence for different types of non-bonded contacts. Desired information is presented in the form of scatter-plots showing the spatial distribution of non-bonded contacts between the 'central' and the 'contact group'. Those data for 'central groups' (terminal substituents, acyclic linking groups, heterocyclic ring systems) interacting with many types of 'contact groups' (hydrogen bond accep-

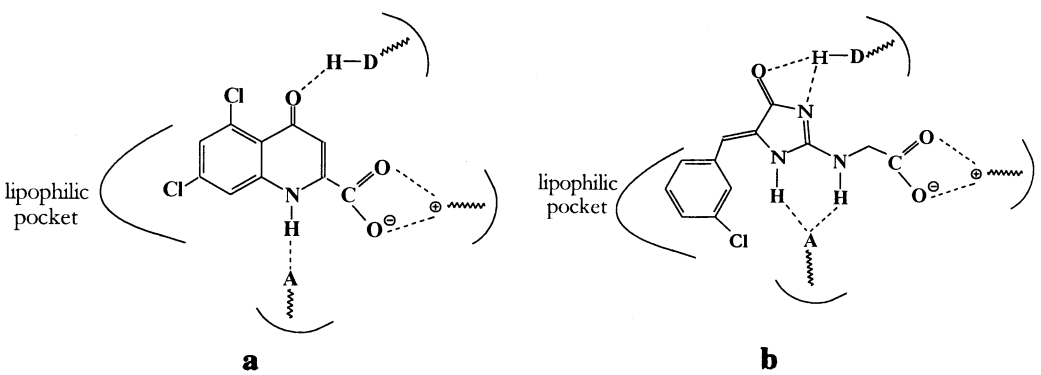


Fig. 1. Glycine binding site for the kynurenic acid molecule and arylideno-imidazolinonoyl-glicynes.

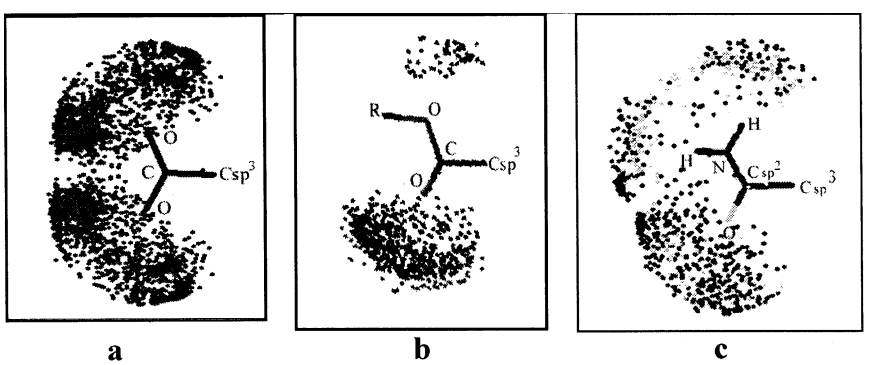


Fig. 2. Surfaces of crystallographically registered interactions with H–X (X = O, N) species for: (a) COO^-; (b) COOR; (c) $CONH_2$.

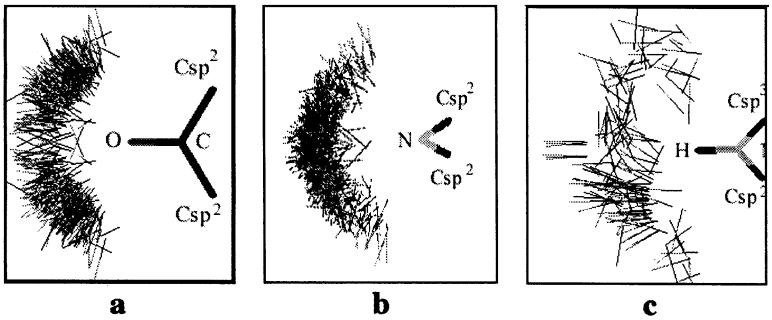


Fig. 3. Surfaces of crystallographically registered interactions for: (a) C = O···H–D (D = N, O, C); (b) N(endocyclic sp)···H–D (D = N, O, C); (c) N–H···A (A = N, O, C).

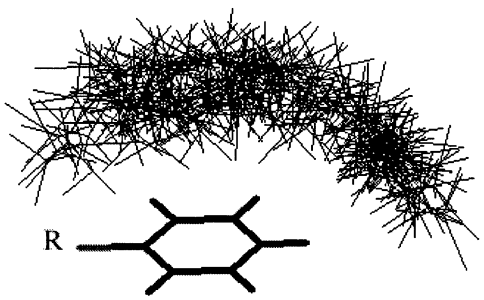


Fig. 4. Surfaces of crystallographically registered phenyl···H–C interactions region (for clarity only one half of the shell is given).

tors, hydrogen bond donors, hydrophobic groups, ions, etc. from the receptor) helped us to rationalise the specific site point.

Acknowledgements

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