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Spacer conformation in biologically active molecules*

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Abstract: Based on our contemporary studies on the structures of biologically active molecules, we focus our attention on the aliphatic chain and its conformation. That flexible spacer definitely influenced the balanced position of all pharmacophoric points in molecules of biological ligands. The one atomic linker and two or three atomic spacers with one heteroatom X = O, S, CH_2, NH have been taken into account. The conformational preferences clearly depend on the heteroatom X. In the discussion, we utilize our own X-ray data, computation chemistry methods, population analysis, and statistical data from the Cambridge Structural Database (CSD).

INTRODUCTION

Despite the biological activity profile, from a structural viewpoint, all biological ligands can be arranged into two sets. The first one comprises conformationally inflexible molecules with all pharmacological important points in their rigid skeleton. In these molecules, the aliphatic chain, if present, influences only the physicochemical properties. The determination of biologically active conformation in these objects is usually not very complex. However, in the second subset of the ligands, pharmacophoric groups (aromatic rings or H-bond participants) are joined by a flexible aliphatic chain containing one or even more (practically maximum four) atoms (Fig. 1). That aliphatic linker is briefly named as a spacer.

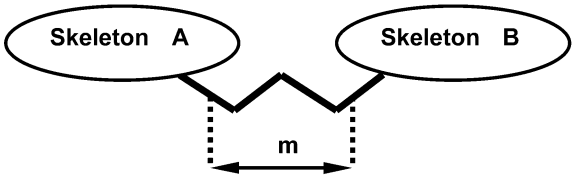

Fig. 1 Aliphatic chain labeled as spacer or distance arm.

In general, the spacer defined in Fig. 1 contains carbon atoms. But very often it comprises also an additional heteroatom, mostly sulfur, oxygen, or nitrogen in the form of the NH group. The total amount of all possible low-energy conformations for that elastic chain depends on the number and nature of the atoms. Theoretically, each bond possesses rotational freedom. So, even if only two bonds (i.e., three atoms) are taken into consideration, the molecule conformation can vary in broad range, from the folded to the extended one. In fact, the mutual position of all pharmacophoric points from skeletons A and B is going to be a function of the spacer conformation. For this reason, from a structural view-

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point, the spacer seemed to be a particularly interesting element of the structures from the set of flexible biologically active molecules.

Having a huge number of our own structures of biologically active molecules, we decided to perform systematic examination for the spacer conformation. From our structural material, three groups of derivatives, with different biological activity, have been elucidated [1–4]. All of them incorporate a more or less complex aliphatic chain. In the series of analogous derivatives, one atom, X, is of the chain varieties (Fig. 2). In general, carbon, oxygen, sulfur, or nitrogen can be placed as X-atom. Depending on the chain, that atom can be at an even or odd position.

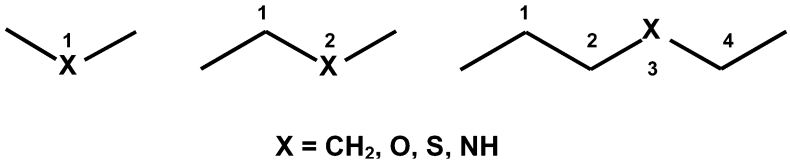
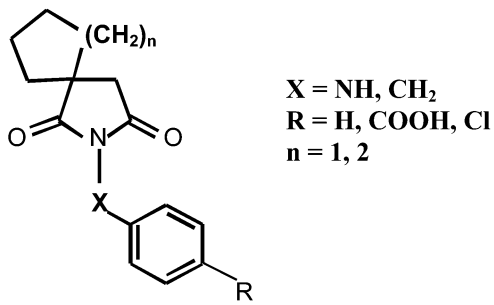


Fig. 2 Selected hetero-aliphatic chains.

At the end, we select groups with one atomic chain as aliphatic linker in succinimides [4] with anticonvulsant activity, short di-atomic spacer found in benzoxazole derivatives with confirmed antifungal activity [1], and molecules with a longer spacer from the class of arylo-piperazines [2,3].

ALIPHATIC LINKER IN SUCCINIMIDES

Our studies on *N*-phenyl-succinimides with anticonvulsant properties has a long history, since 1993 [5]. However, recent development in the synthesis gave us the compounds with NH or CH_2 as distance linker between endocyclic nitrogen and phenyl [4]. Based on crystallographically studied crystals, it was stated that an H-bond net in the crystals depends on the nature of X-atom (Scheme 1).



Scheme 1

For compounds with NH group in linker, a strong H-bond of O1….HN joins molecules in the crystal. No H-bonds with the second oxygen were localized. On the other hand, for species with CH_2 group in linker, weak H-bond interactions are restricted for O2 atoms of O2…HC. Once again, no H-bonds with the remaining oxygen were localized. Therefore, H-bonds net indicates nonequivalency of O1 and O2 from succinimide ring (Fig. 3).

It is of wider interest that from our previous studies with phenyl-succinimides [5] we know that active and inactive compounds could be differentiated based on minimal molecular electrostatic potential (MEP) close to both carbonyl oxygens. Different H-bond patterns (Fig. 3) for different linking atoms in the present study suggest that the X-atom nature reflects also on those minimal depths. In consequence, it may reflect on the compound activity.

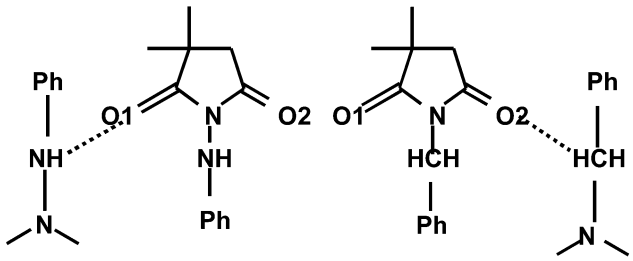
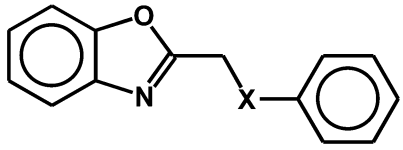


Fig. 3 H-bonds in succinimides with different linking atom X.

BENZOXAZOLES: MOLECULES OF TWO-ATOMIC DISTANCE ARM

A two-atomic spacer is present in benzoxazoles (Scheme 2). It should be mentioned that the spacer seems to be important for antifungal activity of benzoxazoles, as the previously studied inflexible analogs, without any spacer, were found to be less active [6]. For these studies, still in progress, a broad spectrum of heteroatom X is available. The conformation of the spacer in the molecules with sulfur is (–) synclinal, while that with oxygen is (+) antiperiplanar. Therefore, the conformation of a simple two-atomic spacer $–CH_2–X–$ strongly depends on the X-heteroatom in benzoxazole derivatives under discussion, which reflected on the mutual position of two aromatic parts in the molecule, determined by a distance between the centers of two aromatic fragments of the molecule. When the spacer adopts synclinal conformation in derivatives with X = S, that distance equals about 6 Å. At the same time, when X = O, and the antiperiplanar spacer conformation was observed, the named distance increases to about 8 Å (Fig. 4).



Scheme 2

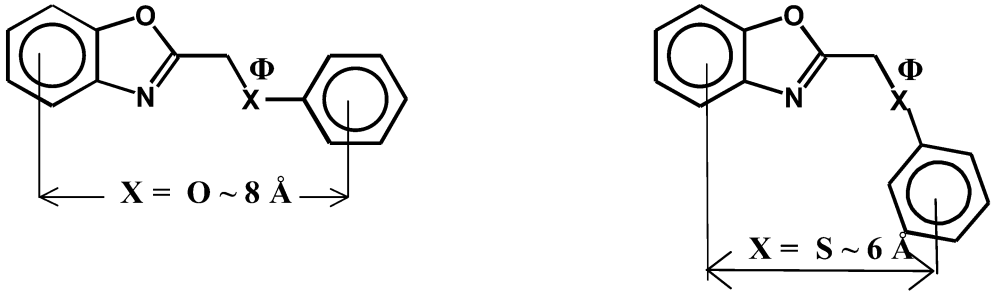


Fig. 4 Distances between aromatic parts in benzoxazoles with different atom in the spacer.

On the other hand, statistical data from CSD [8] for aliphatic chain (cycl)C–CH_2–X–C(arom), cited in Table 1, indicate that spacer containing sulfur with almost equal probability adopts both conformations—synclinal and/or antiperiplanar—in the crystals. For structures with spacer-containing oxygen, the conformations found with respect to $|\Phi|$, with evident predominance, are the antiperiplanal one (Table 1). Therefore, for structures collected in the Cambridge Structural Database (CSD), the anti-

periplanar conformation dominates in derivatives with $–CH_2–O–$. However, $–CH_2–S–$ can be either synclinal or antiperiplanar. It should be noted that excellent agreement was found between the conformational calculations for benzoxazole molecules and statistical data for the structure obtained from CSD.

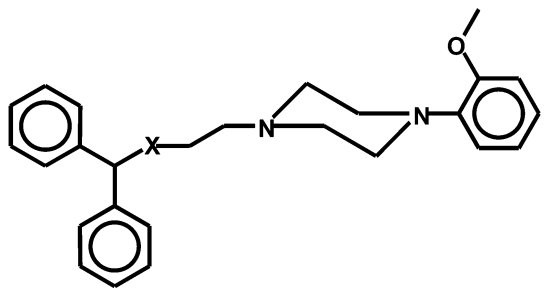
Table 1 Torsion angle Φ (Fig. 6) value for conformational studies of two-atomic chain $–CH_2–X–$ conformation in benzoxazoles (preferred values are given in bold).

Method of the study	Φ = (cycl)C–CH_2–X–C(arom) [°]	
	X = S	X = O
X-data [1]	–70	180
Conformational energy distribution [7]	±80 or ±180	±80 or **±180**
CSD searches [8]	±80 or ±180	±80 or **±180**
Concluding preferences	±80 or ±180	±180

As it was established, the conformation of a simple two-atomic spacer $–CH_2–X–$ strongly depends on the X-heteroatom nature. In consequence, the mutual position of two aromatic parts can be dramatically different. This observation is important for future work on designing the new derivatives for pharmacological screening.

ARYLO-PIPERAZINES WITH $–CH_2–CH_2–X–CH_2–$ CHAIN

Fruitful results have inspired us to study ligands with aliphatic chain containing more than two atoms, and a designed hetero-aliphatic spacer was found in two analogous molecules (Scheme 3).



X = O, NH

Scheme 3

Molecules selected just now contain four-atomic spacer $(N)CH_2–CH_2–X–C(sp3)$ with one heteroatom X. It is noteworthy that both compounds exhibited a different pharmacological profile. The compound with X = NH has been classified as the postsynaptic 5-HT1A receptor antagonist, while the compound with X = O demonstrated some agonistic properties at presynaptic 5-HT1A receptors [3].

The studied compounds are very similar to each other, and both incorporate two border aromatic groups: on one side—(2-methoxyphenyl)piperazine and on the other—diphenylmethyl. The aliphatic chain joins named boundaries and is a focal point in our discussion. Aliphatic chain, equatorial substituent at piperazine nitrogen, adopts fully extended (antiperiplanar) conformation with X = NH and gauche (synclinal) one for X = O. The differences in the conformation of both chains are clear from Fig. 5. In both molecules, this aliphatic chain contains four atoms, one of which is non-carbon (NH or O). The conformation of the chain has determined the distances between the analogous points in the molecules. In the studied molecules, this distance between the oxygen atom from 2-methoxy substituent and heteroatom from the chain equals 8.37 Å in the molecule with X = NH, but it is shorter in the bend

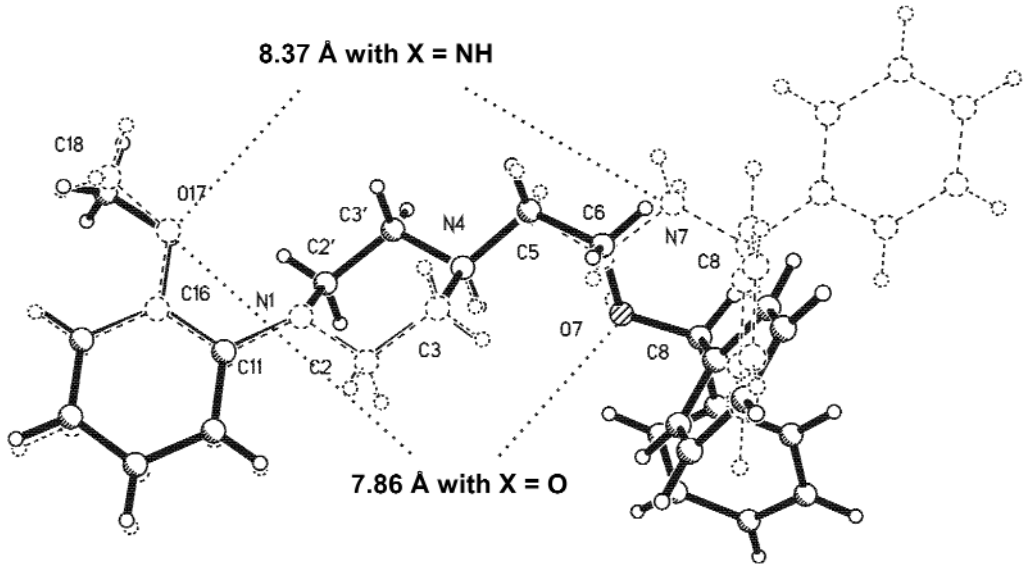


Fig. 5 Superimposition of two molecules with different X-atom in the spacer.

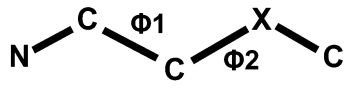
chain for X = O being equal to 7.86 Å. The last conclusion might be important for explaining a disagreement with respective pharmacophore model. Therefore, one can assume that the source of different pharmacological profiles for both compounds could be related to nonidentical conformational preferences of both molecules. The results of all methods applied in this study for elucidating the conformational preferences of the four-atomic non-all-carbons linking chain (N)C–C–X–C are gathered in Table 2 and all are going to lead to a similar conclusion.

Table 2 The torsion angles values (Fig. 9) selected for conformational studies of four-atomic chains (N)C–C–X–C.

Method of the study	Torsion angles in (N)C–C–X–C chain [°] with			
	X = NH		X = O	
	Φ1	Φ2	Φ1	Φ2
X-data [3]	–177.8	–180.0	53.5	–163.5
			65.2	–170.2
Conformational energy distribution [7]	±60 or ±180	±180	±60	±180
Random search surface examination [9,10]	±180	±180	±60	±180
CSD searches [8]	±180	±180	±60	±180
Concluding preferences	±180	±180	±60	±180

In our studies on four-atomic spacer conformations, we employed statistical data from CSD. Review was done for two noncyclic sequences of atoms N(sp^3)–C(sp^3)–C(sp^3)–X–C(sp^3), where X = NH and/or O. The search was perform for two-torsion angles, as in Scheme 4. Analogous two-torsion angles were also accepted in conformational studies. The most prevalent values of torsion angles in the crystals are in full agreement with conformational studies.

It seems to be clear from Table 2 that the preferred conformation depends on the nature of the X-atom. The preferred conformation for the chain with X = NH has been fully extended, while that for chain with X = O—the bend one. For both studied chains, named optimal conformations coincide with that observed in the crystal.



Scheme 4

CONCLUSIONS

At the end, we can formulate three concluding remarks:

- For m = 1, linking atom X has influenced the electronic properties of the atoms in the molecule. In our example, it was demonstrated as different privileges for H-bond acceptors in the molecule.
- For m > 1, conformation of the chain depends on the heteroatom X nature and position.
- The chains with the same X-atom in even and odd positions are not identical. It was demonstrated for X = O. Two-atomic chain with X = O in even position possesses extended conformation. Four-atomic chain with X = O in uneven position is bend.

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