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New Sterically Driven Mode for Generation of Helical Chirality

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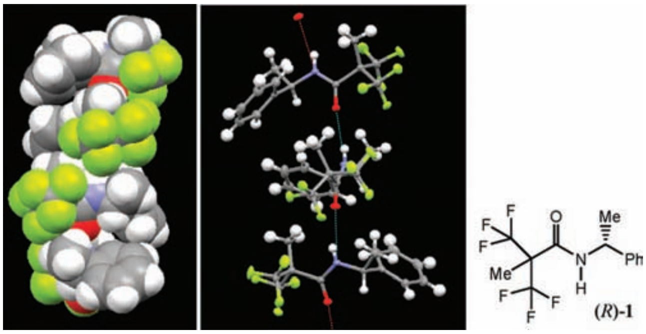
ABSTRACT



The presented results and the available literature data convincingly suggest that there is a new sterically driven mechanism for the formation of supramolecular helicity in the solid state. This mechanism requires the presence of sterically bulky groups, such as *tert*-butyl, for which the spiral arrangement in uninterrupted hydrogen-bonding chains, serving as an axis for helical structure and maximizing the repulsive stereochemical interactions, provide for the most efficient, spatially economical accommodation of these groups in a crystallographic unit cell.

The helix is one of the most fascinating structures in Nature, making use of all three spatial dimensions (an axial chirality) and time (a direction in space). Its paramount structural importance in the biological evolution is manifested by key biological molecules, such as nucleic acids[1] and peptides[2] in which the helicity predetermines their higher-order structures and elaborate biological functions. A huge scientific effort has been devoted to understand[3,4] and mimic[5] this nature-favored conformation. The formation mechanisms of helical conformation have been explained by the geometrically motivated model[3] and the entropically driven model.[4] Here we report a possibly new, sterically driven mode for the formation of helical chirality in the solid state. It is based on the most economical spatial accommodation of sterically bulky groups in a crystallographic unit cell. One important condition for realization of this sterically driven mechanism is the formation of uninterrupted hydrogen bonding, putting the molecules in close proximity to each other, thus increasing the impact of the repulsive stereo-

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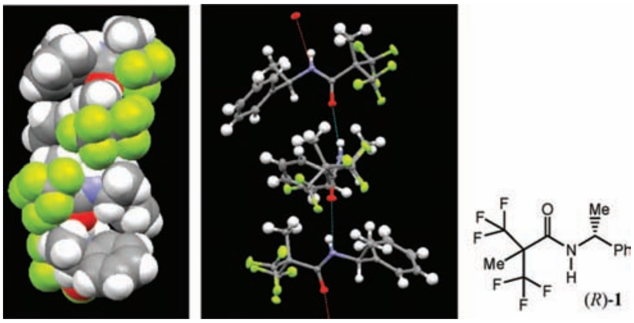

Figure 1. Molecular and crystallographic structure of amide **1**.

chemical interactions. This sterically driven mode seems to be of quite general nature as it can be applied for predictable generation of the corresponding helical structures from compounds possessing as well as lacking molecular chirality.

In the course of our research on the phenomenon of self-disproportionation of enantiomers,[6,7] we have studied physicochemical properties of several chiral amide derivatives containing highly bulky and/or electron-withdrawing moieties. Thus, to study a pattern of hydrogen-bonding interactions in the solid state, we conducted systematic crystallographic analyses of the corresponding racemic and enantiomerically pure forms. In particular, the X-ray analysis of amide **1** (Figure 1), derived from (*R*)-α-(phenyl)ethylamine and hexafluoro-pivalic acid, has revealed a very well organized helical arrangement of amide **1** molecules connected via infinite hydrogen bonding between the amidic N−H and C═O functionalities. Only right-handed [of (*P*) absolute configuration] helixes where found in this structure, suggesting a stereochemically complete transfer of the molecular central chirality into the macromolecular helical chirality.

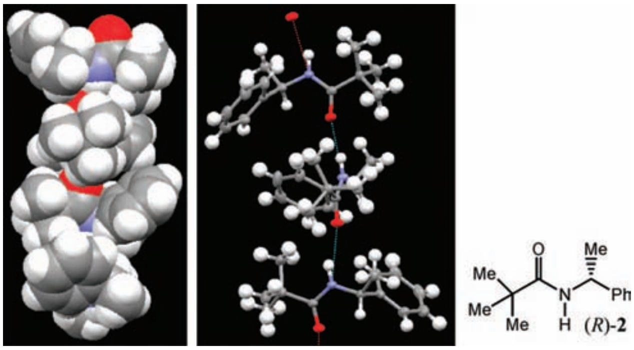

Figure 2. Molecular and crystallographic structure of amide **2**.

To rationalize the formation of the observed helical structure we assumed that the huge steric bulk of the hexafluoro-*tert*-butyl group [$CH_3(CF_3)_2C$],[8] as well as strong electrostatic and polarizing properties of the trifluoromethyl groups[9] may be of special importance in this particular case. To generalize this observation and also to separate the fluorine effects from the steric bulk effect we prepared the amide **2** (Figure 2), derived from the same (*R*)-α-(phenyl)ethylamine and fluorine-free pivalic acid. To our delight, the X-ray analysis of the derivative **2** revealed its helical structure in the solid-state. The absolute configuration of the helical chirality was found to be *P*, in accord with helicity of the amide **1**, suggesting that molecular (*R*)-absolute configuration of the amine residue was reliably transferred into (*P*)-configuration of the macromolecular helical structure.

As the next logical step, it was very important to investigate if the helical structure could also be formed without the presence of the molecular chirality in the starting compound. To this end we prepared achiral amide **3** (Figure 3), derived from benzylamine and pivalic acid. Surprisingly, the X-ray analysis of amide **3** revealed its beautiful helical structure in the solid state. In this case, the crystal unit cell consisted of 8 molecules equally representing *M* and *P* helixes (only left-handed *M* helix is shown in Figure 3).

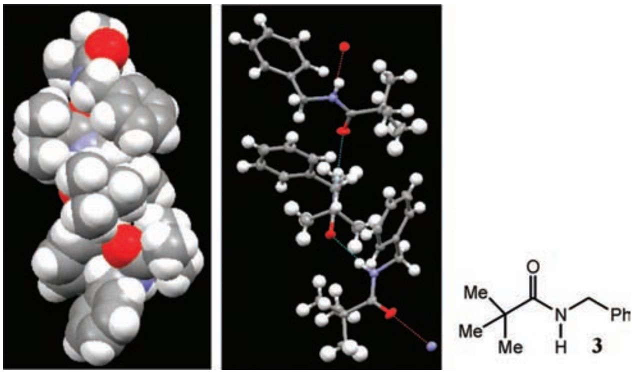

Figure 3. Molecular and crystallographic structure of amide **3**.

These results suggested that steric bulk of the *tert*-butyl group is solely responsible for the observed formation of helical chirality in the solid state, regardless of the presence or absence of molecular chirality in starting compounds. This property is

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(6) Via ap-chromatography:(a) Soloshonok, V. A. *Angew. Chem., Int. Ed* **2006**, *45*, 766–769. (b) Soloshonok, V. A.; Berbasov, D. O. *J. Fluor. Chem.* **2006**, *127*, 597–603. (c) Soloshonok, V. A.; Berbasov, D. O. *Chim. Oggi/Chem. Today* **2006**, *24*, 44–47.

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quite rare, but of significant importance in functional crystal engineering and supramolecular chemistry.[10]

With these results in hand, we decided to further investigate importance of the steric factor of a *tert*-butyl group. Therefore the effect of a gradual reduction of the steric bulk of a *tert*-butyl group on the supramolecular structure in the solid state was studied. To this end we prepared the corresponding amide **4** (Figure 4), derived from benzylamine and 2-(methyl)propionic acid, containing less sterically bulky *iso*-propyl group instead of *tert*-butyl group. The result of the X-ray analysis of the amide **4** was quite conclusive. The molecular structure of derivative **4** was found to be achiral, as molecules of less sterically demanded *iso*-propyl containing **4** found the way of packing in more compact parallel arrangement.

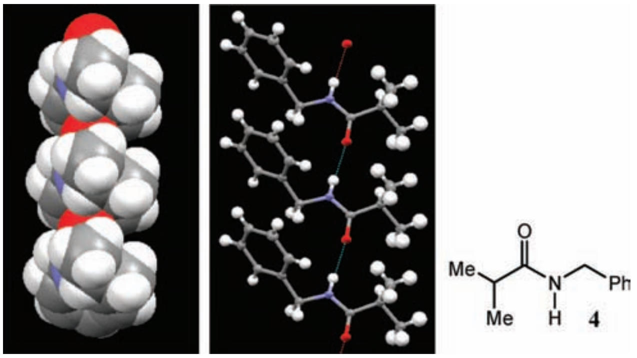


Figure 4. Molecular and crystallographic structure of amide **4**.

These results clearly demonstrated a key importance of the presence of a *tert*-butyl group in the starting compound for generation of helical chirality in the solid state.

Finally, we were delighted to find that available literature data are in full accord with our results and therefore provide an additional support of our hypothesis of a new sterically driven mode for generation of helical chirality in the solid state. Thus, Lait et al. reported synthesis and crystallographic structure of pivalic acid derived amides **5a** and **5b** (Figure 5).[11] Both compounds **5a** and **5b** showed exclusively (*M*)-helical arrangements along the hydrogen-bonding axis of the amide functionality. Since the compounds **5a** and **5b** contain multiple stereogenic centers, it is not possible to rationalize the effect of their absolute configuration on the sense of the generated helical chirality.

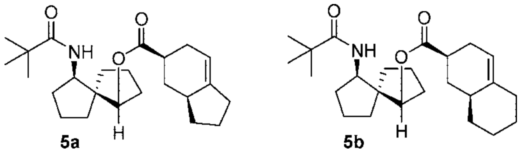
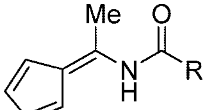


Figure 5. Literature example of helical structure in the solid state of pivalic acid derived amide containing molecular chirality.

Another example, reported by Duda et al., is even more significant as it supports our conclusion about key effect of the steric bulk as well as possibility to generate supramolecular helicity in the solid state without the molecular chirality in the starting compounds.[12] Thus, amides **6a** and **6b** (Figure 6), derived from acetic and *p*-(methyl)benzoic acids, respectively, gave achiral, parallel arrangement of hydrogen bonded molecules. On the other hand, compound **6c**, containing a sterically demanding *tert*-butyl group, generated supramolecular helicity in the solid state.



6a-c

R = Me (**a**), *p*-Me-C_6H_4 (**b**), *tert*-Bu (**c**)

Figure 6. Literature example of helical structure in the solid state of pivalic acid derived amide lacking molecular chirality.

Furthermore, the detailed analysis of the available crystallographic data clearly pointed out the importance of the formation of an uninterrupted, infinite hydrogen-bonding network between the molecules, providing the corresponding axis for the helical arrangement of sterically bulky groups around it. For instance, in the case of compounds containing, besides the *tert*-butyl group, multiple functionalities such as hydroxy, free carboxy, or amino groups, which interfere with the formation of proper one-dimensional hydrogen bonding network, the corresponding helical structure in the solid state was not observed.[13] A similar result was found for *tert*-butyl-containing compounds that cocrystallize with molecules of protic solvent such as water or alcohol. Upon being incorporated into the crystallographic structure, these hydroxy group containing molecules interfere with the formation of the proper hydrogen bonding network and obstruct the realization of the sterically driven helical structure.[14]The importance of the formation of a proper hydrogen-bonding network is, probably, most clearly manifested from the crystallographic structures of pivaloyl amides prepared from secondary amines, which cannot form the required hydrogen bonding network and therefore the corresponding macromolecular helicity in the solid state.[15]

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In conclusion, the results presented here, as well as the available literature data, convincingly suggest that there is a new sterically driven mechanism for the formation of supramolecular helicity in the solid state. This mechanism requires the presence of sterically bulky groups, such as *tert*-butyl or larger, for instance a hexafluoro-*tert*-butyl, for which the spiral arrangement in the uninterrupted hydrogen-bonding chains, serving as axis for helical structure and maximizing the repulsive stereochemical interactions, provide for the most efficient, spatially economical accommodation of sterically bulky groups in a crystallographic unit cell. Furthermore, this mechanism can be applied for generation of supramolecular chirality from the compounds possessing as well as lacking molecular chirality. Taking into account synthetic simplicity of introduction of *tert*-butyl containing moieties into organic molecules, this new approach can find generalized application and make a practical advance in the currently fast-expanding areas on functional crystal engineering and supramolecular chemistry.

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Supporting Information Available: Synthesis and spectrascopic data for compound **1** and crystallographic structure determination for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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