Articles

A Spectroscopic and Crystallographic Investigation of the Structure and Hydrogen Bonding Properties of the Chiral Leukotriene Antagonist MK-679 As Compared to Its Racemate MK-571

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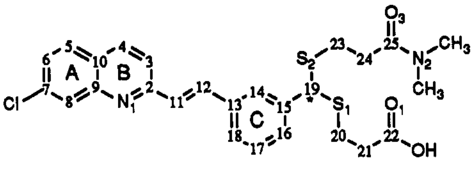
The crystal structure of (*R*)-(−)-3-[[[3-[2-(7-chloroquinolin-2-yl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propanoic acid has been determined; $C_{26}H_{27}ClN_2O_3S_2$, $M_r = 515.10$, $P2_12_12_1$, $a = 19.379$ (3) Å, $b = 25.298$ (5) Å, $c = 5.0539$ (8) Å, $Z = 4$, $F(000) = 1080$, $T = 296$ K. The molecules form hydrogen-bonded chains along the *b* axis and exhibit $\pi-\pi$ stacking interactions of their extended π-systems. Solid-state infrared and CP/MAS ^{13}C NMR spectra of the this compound and two polymorphs of its racemate are compared, and correlations are made between the spectral features and the structures of the solids. The spectra are different and can be used to positively identify each of the crystalline forms.

Introduction

The current model[1,2] for asthma invokes a mixture of leukotrienes (LTC_4, LTD_4, and LTE_4) as the important mediators with the receptor for LTD_4 being a pharmacologically relevant target.[2] Since the identification of this target there has been considerable interest in developing effective and therapeutically useful LTD_4 antagonists both as potential antiasthma drugs and to assess the correctness of this asthma model.[3,4]

Both the racemic and the enantiomerically pure forms of the unsymmetrical dithioacetal, 3-[[[3-[2-(7-chloroquinolin-2-yl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propanoic acid, have been shown to be effective leukotriene D_4 antagonists.[5-7] We are interested in the structure of the *R* enantiomer of this compound, MK-697 (1), in order to relate its solid-state packing and hydrogen bonding to its NMR and infrared spectra, and to compare and contrast these data and observations with similar information for the two known polymorphs of the racemate (MK-571).[8] The crystallographic investigation of the polymorphs of MK-571 is being undertaken in another laboratory.[9]



1 * = *R*
MK-571 * = *R*, *S*

Experimental Section

Crystals of 1[10] suitable for X-ray analysis were grown by slow evaporation of a filtered solution of 1 in isopropyl alcohol, held at 45 °C in a loosely capped amber vial, which was protected from light.[11] Crystals of 1 used for infrared and solid-state NMR spectroscopy were harvested from this same crop and ground to a fine powder using a mortar and pestle. Finely divided crystals of form I and II of the racemate were grown from ethanol and methyl ethyl ketone, respectively.[8] Infrared spectra were obtained on a 60-SX spectrometer using a microscope attachment, while solid-state ^{13}C CP/MAS NMR spectra were obtained at ambient temperature on a GN 300 spectrometer.

Crystallography. Data were collected on an CAD4F diffractometer using graphite-monochromatized Cu Kα radiation. During data collection no significant change in the intensity standards wwas observed. The structure was solved using SHELXS-86[12] (determination of the absolute configuration was not required) and refined using full-matrix least-squares based on *F*. Reflection weights were defined as $1/\sigma^2(F)$. Data were corrected for absorption using the approach of Walker and Stuart.[13] The refinement model has all non-H atoms refined with anisotropic temperature factors; all H atoms (excepting the hydrogen of O1) are included at their calculated (C–H 0.95 Å, sp^2 or sp^3 geometry) positions. The thermal parameters of the H atoms are defined

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(9) We thank Prof. Byrn, Purdue University, for providing us with access to crystallographic data on form I of MK-571 prior to publication.

(10) We thank Dr. Mahadevan Bhupathy, MSDRL Process Research, for providing samples of MK-679 and MK-571.

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to be 1.2 times those of the attached atom; during refinement the positional parameters of the H atoms were constrained to ride with those of the attached atom. The maximum peak height in a final difference Fourier is 0.37 (4) e Å^{-3} (0.482, 0.047, 0.416) and is without chemical significance. The final R and wR values are 0.041 and 0.038, respectively. All calculations were performed using SDP-Plus software.[14] The experimental parameters are presented in Table I, while Table II contains the refined atomic positional and thermal parameters and bond distance and angles are listed in Table III; the crystallographic numbering scheme used is shown in 1 (please refer to the supplementary material for tables and figures not included in the body of the paper).

Results and Discussion

The molecule adopts a structure which is approximately T-shaped, where the two arms of the T are formed by the thioacetal substituents, while the quinoline group, the phenyl ring, and the ethenyl double bond form the stem of the T. The crystal structures of quinoline and substituted quinolines have been well studied with some attention paid to the effect of various substituents on the bonding within the group. For the quinoline moiety in the present structure we have compared the observed bond distances with those of 80 other structures (drawn from the Cambridge Structural Database[15]) and with the distances reported for theoretical calculations using the PPP (Pariser–Parr–Pople) method.[16] The results of this comparison show that, in general, the experimentally determined bond lengths closely mirror the theoretical results, and this is especially so if the *pattern* of the bond distances is considered rather than the precise magnitude of each distance (see supplementary material for a tabulation of distances). The extended π system, formed from the three aromatic groups and the ethenyl double bond, is generally flat with only small angles (maximum is 9.1°) between the mean planes of the various moieties comprising it. The remaining distances and angles in the structure are all within ranges typical for the respective bond types.

Comparison of the structures of 1 and MK-571[17] shows there to be no significant differences in bond lengths or angles which is what would be expected for the comparison of the structure of a single enantiomer versus its racemate. There is, however, one major conformational difference between the structures of the two compounds; ring C adopts two different positions, related by a 2-fold rotation about the bond linking this ring to the ethenyl double bond. For the isolated molecule the two orientations of this ring are presumably very similar in energy but, as discussed below, the type of hydrogen bonding in the crystal is strongly affected by the tertiary structure of the molecule.

The main focus of our interest in the structure of 1 is the solid-state packing and hydrogen bonding within the crystal and, in turn, how this relates to the observed spectroscopic results. As shown in Figure 1a the molecules in 1 form π–π stacking interactions of the extended, unsaturated systems of adjacent molecules. The mean planes of the aromatic systems of these molecules are 3.52 Å apart, the usual distance for this type of interaction, and are staggered with respect to the overlap such that the π-system of one molecule lies over the π-cavity of the other.[18] As shown in Figure 1a all three elements of the extended π-system of 1 are involved in the interaction. In the crystal of MK-571 the molecules also stack (Figure 1b) but with a somewhat closer mean plane-to-plane distance of 3.3 Å; however, the overlap is not as complete as is the case in 1. As shown in Figure 1b, only the quinoline moiety and the ethenyl double bond of MK-571 participate in the stacking interaction. This apparently allows the phenyl ring more freedom since it makes a considerably larger angle with respect to the plane of the quinolyl group (23.3°) than is the case in 1 (5.6°).

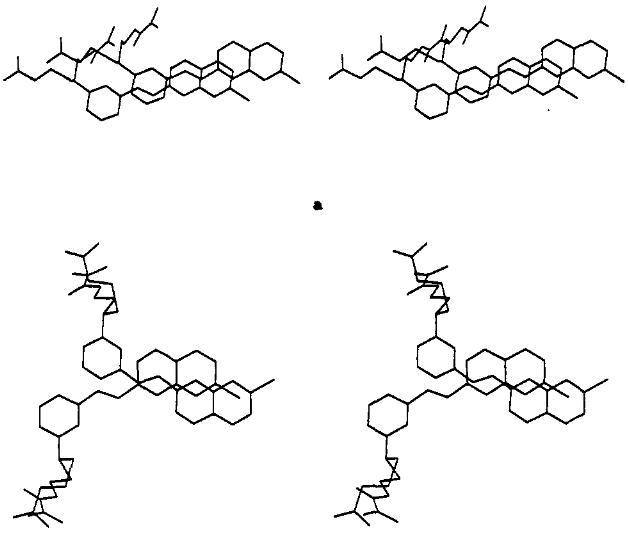

Figure 1. (a) Extended π-systems of two adjacent molecules of 1 form a stacking interaction and show an extensive overlap. (b) Adjacent molecules of MK-571 also participate in a stacking interaction but with a much smaller degree of overlap of the extended π-systems.

In the solid state, compound 1 forms extended chains of hydrogen-bonded molecules with the hydroxyl of the acid acting as a donor to the quinoline nitrogen of a symmetry-related molecule. The bond is quite strong with an N_1–O_2 distance of only 2.679 (5) Å. This pattern is repeated in extended chains along the *b* axis of the unit cell. In MK-571, however, the hydrogen bonding motif is quite different; in this case the molecules form *R*,*S* pairs with the OH of each acid acting as a hydrogen-bond donor for its partner's quinoline nitrogen. The N–O distance in this case is 2.647 (8) Å indicating this also is a strong hydrogen bond. One can categorize the differences in these hydrogen-bond motifs using Etter and Bernstein's graph-set encoding.[19,20] Racemic MK-571 has two donors and two acceptors in its repeating motif, which is a ring of 28 atoms; thus, its graph-set representation is $R_2^2(28)$. In the single-enantiomer species, 1, the hydrogen-bond repeat unit is a chain of 14 atoms with one donor and one acceptor, and its graph-set representation is C(14). Rings can have inversion centers, and thus be made of an *R*,*S* pair of molecules. Unless the molecule itself is centric, which is not the case here, chains cannot have an inversion center. It is the conformational difference between 1 and MK-571, mentioned above, which permits the ring versus chain configuration of the hydrogen bonding. If the phenyl ring bearing the thioacetal substituents is not flipped over from its position in 1 then the groups are not positioned such

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that the observed hydrogen bonding can occur.

The effects of the intermolecular hydrogen bonds can be seen in the infrared spectrum of 1. In dilute solution ($CDCl_3$), the amide stretch is at 1632 cm^{-1}, as expected for a tertiary amide,[21] the carboxylic acid stretch is at 1733 cm^{-1}, and there is no evidence for protonation on the quinoline ring. The spectrum of crystalline I has two broad absorbances centered at 2480 and 1880 cm^{-1}, characteristic for a protonated imine. The carboxylic acid stretching frequency is lowered when compared to the dilute solution spectrum, to 1698 cm^{-1}, diagnostic of its participation as a donor in a hydrogen bond. The amide carbonyl infrared band in the crystal is strong, presumably due to the increased polarizability of this bond as a result of the dipole attractions arising from the molecular stacking orientation, and split into two bands at 1638 and 1625 cm^{-1}. This is analogous to the splitting seen in the infrared spectra of solid crystalline chiral carboxylic acids as reported by Wallborsky et al.,[22] where a similar splitting of the carboxylic acid stretch is attributed to stretching modes which become IR active because of the proximity of the functional groups in the solid and the symmetry of the crystal. In the solid, the amide carbonyls will have both an asymmetric and a symmetric stretching vibration, with the symmetric vibration being infrared-active only in the chiral material. This should also be true for the acid carbonyl, but the presumed two bands are not resolved.

The crystalline racemate MK-571 has two polymorphs designated form I and form II.[8] The structure at 170 K of form I has been solved,[17] but efforts to grow a suitable single crystal of form II have proven unsuccessful to date. As is the case for 1, structural features are evident in the infrared spectrum. In form I, the broadened iminium-like signals are centered at 2480 and 1980 cm^{-1}, the carboxylic acid carbonyl appears at 1714 cm^{-1}, and the amide carbonyl has a single band at 1651 cm^{-1}. Form II exhibits the same iminium-like signals centered at 2480 and 1920 cm^{-1}, with its acid at 1703 cm^{-1} and amide at 1635 cm^{-1}. We speculate that the solid-state structure of form II will also have an intermolecular hydrogen bond from the acid of one molecule to the quinoline ring of its neighbor, but the details of the crystal packing and molecular conformation await a suitable crystal for a complete structure determination. The fingerprint region of the infrared spectra of these three compounds is quite diagnostic. The differences among them, which are reliably reproducible, are due solely to differences in intermolecular interactions in the crystal and differences in crystal symmetry, as their spectra in solution are identical. Solid-state infrared spectroscopy is thus a powerful tool for the straightforward verification of crystal morphology in the case of these three homologues, even on a very small sample size such as that used in infrared microscopy.

The solid-state NMR spectra also provide a diagnostic probe of differences in crystal morphology, but larger sample quantities (250–300 mg in this case) are needed. The ^{13}C solid-state CP/MAS NMR spectra of forms I and II of MK-571 and of 1 show differences in chemical shifts, as would be expected,[23] and the signals for 1 are much sharper than those of either polymorph of MK-571. This may be due to differences in the quality or stability of the crystal lattice since we know, for example, that the single-crystal X-ray structure of MK-571 (form I) had to be done at −100 °C because of crystal instability in the X-ray beam and that the peaks in the X-ray powder diffraction spectra are broader for either form of MK-571 than they are for 1.[24] From the NMR data none of the three appears to have a hydrogen bond to the amide carbonyl, as they are not significantly shifted from the solution value of 170.2 ppm, or from each other.[25]

X-ray crystallography, infrared spectroscopy, and solid-state NMR spectroscopy are all powerful tools for the characterization of organic molecules in the solid state. By combining these tools we can learn much about the nature of molecular interactions. Interactions between functional groups can be seen both crystallographically and spectroscopically. In the best case, when all three methods can be brought to bear, we are able to assign specific spectroscopic features to particular structural details. In other cases, where the crystallographic information is not available, useful conclusions can often be drawn from the spectroscopic results alone, especially if extrapolations from similar structures are feasible.

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Supplementary Material Available: Crystallographic experimental details (Table I), atomic positional and thermal parameters (Table II), bond distances and angles (Table III), comparison of quinoline fragments (Table IV), crystallographic planes (Table V), Figures 2 and 3 (ORTEP plot of the molecule and unit cell packing diagram, respectively), and solid-state IR and NMR spectra (Figures 4 and 5, respectively) (9 pages). Ordering information is given on any current masthead page.

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