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Persistency of a Two-Fold Embrace in Crystalline Phases of Bupropion Hydrohalides: A Thorough *ab Initio* X-ray Powder Diffraction Study

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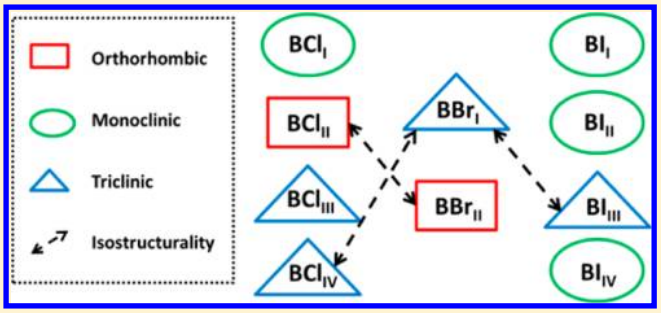
Supporting Information

ABSTRACT: Bupropion hydrohalide salts yield ten different crystal phases of bupropion (four hydrochloride, two hydrobromide, and four hydroiodide salts). Of these forms, only four have been previously characterized by single crystal or powder diffraction analysis. The structures of the six new crystal forms have been solved using state-of-the art structural powder diffraction methods. All ten phases have been found to be made up of the same supramolecular synthon packed in different ways. The supramolecular synthon common to all phases is a bupropion hydrohalide dimer held together by hydrogen bonding. The true driving force of the polymorphism of bupropion hydrohalides is therefore the ability of the bupropion hydrohalide dimer to pack in several different ways and not the ability of the molecule to form different hydrogen bonding motifs or to exist with aliphatic branches in different stable conformations.



1. INTRODUCTION

Polymorphism, the ability of a substance to exist in different crystalline forms, is very important in the pharmaceutical industry, because active pharmaceutical ingredients (APIs) frequently exhibit this kind of behavior.[1] Differences in the crystal structures can lead to very different physical and chemical properties, which can influence industrial processability, formulability, and, more important during patient treatment, bioavailability. For example, different crystalline forms can have different solubility, hygroscopicity, flowability, compactability, and chemical and physical stability.[2,3] It is therefore often crucial to know the polymorphic behavior of an API before attempting production and formulation to ensure reproducibility of the process, the extension of shelf life and, finally, the correct therapy. Of course, there are many cases in which polymorphism will not be a safety and efficacy issue for a drug product, for example, in the case of highly soluble APIs, where bioavailability is not impaired by solubility. However, in these cases, the solid state can still have an impact on the processability and formulability of a drug product. Moreover, the fact that solid forms of APIs are patentable makes polymorphism an important factor in the life cycle management of a drug product.

Polymorphism and, more generally, the solid state characterization of drugs can often be a resource for the pharmaceutical industry, as the search for previously unknown solid forms can lead to products with more favorable characteristics than those previously observed. This is true also in the search for different salts of the same API, in the quest for improved physical–chemical properties.[4,5] Even though different salts can have very different properties (typically, solubility), they can often show structural similarities. This implies that structural knowledge on the different crystalline forms can be fruitfully employed to compare isomorphous salts and to address relevant crystallochemical (mostly, stereochemical) differences among their polymorphs. Moreover, a knowledge of which factors contribute to the generation of polymorphism (for example, molecular flexibility or hydrogen bonding ability) can give insight on what to expect from an analogous salt.

Racemic bupropion, or (±)-2-(*tert*-butylamino)-1-(3-chlorophenyl)propan-1-one, shown in Chart 1 in its protonated (ammonium) form, is an atypical antidepressant used mostly as a smoking cessation aid and for seasonal affective disorder (SAD).[6] It is chemically unrelated to tricyclic antidepressants and its neurochemical mechanism of action is not well-known. It is thought to act as a serotonin, norepinephrine, and dopamine reuptake inhibitor.[7] Even though bupropion has a stereocenter and has been successfully separated into the R and S enantiomers, it is generally used as a racemate because the enantiomers undergo rapid racemization.[8] Bupropion, now marketed under several names, was first prepared and studied in the early 1970s.[9] Initially prepared as a hydrochloride salt, it

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Table 1. References and Nomenclature of Bupropion Salts and Polymorphs

solid form	ref	comments	nomenclature used in this paper
bupropion·HCl form I	13		$\mathbf{BCl_I}$
bupropion·HCl form II	14		$\mathbf{BCl_{II}}$
bupropion·HCl form III	*b*		$\mathbf{BCl_{III}}$
bupropion·HCl form IV	*b*		$\mathbf{BCl_{IV}}$
bupropion·HBr form I	15, 16	this form was initially characterized in ref 15 only by XRPD and DSC; subsequently its crystal structure was published in ref 16	$\mathbf{BBr_I}$
bupropion·HBr form II[a]	15	this form was characterized in the patent literature only by XRPD and DSC and corresponds to bupropion·HBr form IV published in ref 16	$\mathbf{BBr_{II}}$
bupropion·HBr form IV[a]	16	the structure here reported corresponds to bupropion·HBr form II published in ref 15	$\mathbf{BBr_{II}}$
bupropion·HI form I	*b*		$\mathbf{BI_I}$
bupropion·HI form II	*b*		$\mathbf{BI_{II}}$
bupropion·HI form III	*b*		$\mathbf{BI_{III}}$
bupropion·HI form IV	*b*		$\mathbf{BI_{IV}}$

[a]Even though form IV of bupropion hydrobromide is described by Hu and co-workers as being different from form II described in the patent literature, we believe them to be the same crystalline forms. A more detailed discussion is reported in the Supporting Information. [b]Unreported.

was later introduced as the hydrobromide salt, reported to be more stable and less hygroscopic.[10] Bupropion hydrochloride belongs, in the Biopharmaceutics Classification System,[11,12] to class I drugs (those possessing high solubility and high permeability), which means bioavailability is not limited by solubility. Polymorphism has therefore little importance in the safety and efficacy of the final product, but can still be crucial for manufacturing and handling issues, particularly at the production and formulation stages.

Both bupropion hydrochloride and bupropion hydrobromide salts have been shown to exist in different polymorphic solid forms. In particular, two different anhydrous and unsolvated forms are known for each of the hydrochloride[13,14] and hydrobromide[15] salts. As previously reported, the hydrochloride and hydrobromide salts show several important structural similarities.[16]

The occasional discovery of a third and fourth bupropion hydrochloride polymorph (later presented) induced us to further analyze the differences and similarities between the solid-state landscapes of bupropion hydrochloride and hydrobromide salts, adding to the discussion the structures of the pharmaceutically uninteresting but structurally relevant hydroiodide salts. Therefore, four different anhydrous and unsolvated polymorphs of bupropion hydroiodide were isolated using tailored preparations and fully characterized by modern structural powder diffraction methods and thermal analysis. Thus, the abundance of bupropion hydrohalide crystal forms being considerably increased, this paper, beyond reporting on the structural characterization of several new crystal phases, includes an extensive crystal-chemical comparison of the ten forms, in which a strict isomorphous character is observed in two cases *only*.

In order to avoid confusion due to the different nomenclature of the different salts and polymorphs used in the literature, Table 1 synoptically summarizes existing and new crystalline forms and, for the sake of clarity, contains both the labeling previously used and that used in this paper. The denominations of the previously known forms have been maintained as much as possible.

2. EXPERIMENTAL SECTION

2.1. Materials. Bupropion hydrochloride (99.9% purity) was supplied by Dipharma Francis, S.r.l. The solvents and other reagents used were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification.

2.2. Preparation of Different Crystal Phases. *2.2.1. Hydrochlorides.* An ethanol solvate of bupropion hydrochloride[17] was obtained by dissolving 2 g of bupropion hydrochloride in 8 mL of refluxing ethanol and cooling the resulting solution in an ice bath to obtain crystallization. $\mathbf{BCl_{III}}$ and $\mathbf{BCl_{IV}}$ were typically obtained as mixtures by desolvation of the ethanol solvate of bupropion. Different desolvation protocols specifically tailored to obtain a mixture rich in $\mathbf{BCl_{III}}$ or in $\mathbf{BCl_{IV}}$ were devised. A mixture rich in form $\mathbf{BCl_{III}}$ was obtained by slow desolvation of the ethanol solvate at room temperature under vacuum. The X-ray powder diffraction (XRPD) of the mixture was recorded after several weeks, and the product was found to be a mixture of $\mathbf{BCl_{III}}$ and $\mathbf{BCl_I}$ (about 15%). A mixture rich in form $\mathbf{BCl_{IV}}$ was obtained during a differential scanning calorimetry (DSC) experiment: after the ethanol solvate was heated in a pierced aluminum sample holder to 110 °C at 10 °C/min under a flow of nitrogen, the DSC pan was opened and a mixture of $\mathbf{BCl_{IV}}$ (85%) and $\mathbf{BCl_{III}}$ (15%) was retrieved. The chemical identity of the sample after thermal treatment was confirmed by ^{1}H NMR analysis (reported in the Supporting Information). Slightly different desolvation experiments yielded mixtures of different compositions, but never pure phases. For the preparation of $\mathbf{BCl_I}$ and $\mathbf{BCl_{II}}$ see our previous work.[13,14]

2.2.2. Hydrobromides. Bupropion hydrobromide was obtained by dissolving 3 g of bupropion hydrochloride in 7 mL of water and adding aqueous KBr at room temperature under stirring until the formation of a precipitate was observed. The mixture was then heated to obtain complete dissolution and slowly cooled to crystallize $\mathbf{BBr_{II}}$. The identity of the halide ion was confirmed by precipitation of the silver halide from a clear aqueous solution of the obtained solid using a 0.1 M solution of $AgNO_3$. The yellow precipitate confirmed the identity of the bromide ion. A monophasic polycrystalline sample of $\mathbf{BBr_I}$ was prepared by dissolving 20.0 g of $\mathbf{BBr_{II}}$ in refluxing isopropanol (100 mL) and water (8 mL) and rapidly cooling the mixture with an ice

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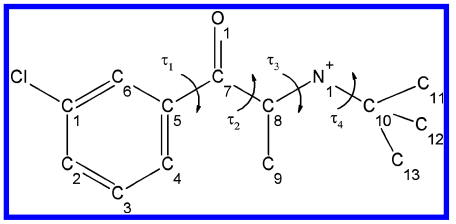
bath. The crystallized solid ($\mathbf{BBr_I}$) was isolated by filtration at 0 °C. As for the other phases prepared in this paper, the structures of $\mathbf{BBr_I}$ and $\mathbf{BBr_{II}}$ were determined using laboratory X-ray powder diffraction methods. Their refined models, however, are not reported here because single crystal structure analyses (needless to say, of much better quality) were recently published.[16] These preparations and the final Rietveld refinement plots for our structure determinations, gathered in the Supporting Information in Figure S2, are therefore given here for completeness.

2.2.3. Hydroiodides. Bupropion hydroiodide was obtained by dissolving 3 g of bupropion hydrochloride in 7 mL of water and adding aqueous KI at room temperature under stirring until the precipitation of a white solid was observed. The solid obtained, recovered by filtration, was a mixture of $\mathbf{BI_I}$ and $\mathbf{BI_{II}}$. The identity of the halide ion was confirmed by precipitation of the silver halide with 0.1 M $AgNO_3$ from a clear aqueous solution. The yellow coloring of the precipitate confirms the halide to be iodide and not chloride. Monophasic $\mathbf{BI_I}$ was obtained by recrystallizing 0.5 g of bupropion hydroiodide in 5 mL of isopropanol and recovering the solid by filtration. Monophasic $\mathbf{BI_{II}}$ was obtained by recrystallizing 0.5 g of bupropion hydroiodide in 2 mL of water and filtering the crystallized solid. $\mathbf{BI_{III}}$ was obtained during a DSC experiment directly in the pierced aluminum pan by heating $\mathbf{BI_{II}}$ under nitrogen flow to 198 °C at 10 °C/min, holding at 198 °C for 6 s, and cooling quickly back to room temperature. The DSC pan was opened and monophasic $\mathbf{BI_{III}}$ was retreived. The chemical identity of the sample after heating was confirmed by ^{1}H NMR (reported in the Supporting Information). Form $\mathbf{BI_{IV}}$ was obtained by dissolving 4.1 g of bupropion hydroiodide in 5 mL of trifluoroethanol. The clear solution obtained was then slowly concentrated at room temperature by evaporation of the solvent under a flow of nitrogen. A white solid crystallized and was recovered by filtration. The sample of form $\mathbf{BI_{IV}}$ used for structure solution contained traces of KI, clearly visible in the powder diffraction trace as weak but sharp peaks.

2.3. X-ray Powder Diffraction (XRPD) Analysis. All samples were analyzed using a 0.2 mm deep aluminum sample holder having a quartz monocrystal zero background plate (supplied by *The Gem Dugout*, State College, PA) or a silicon monocrystal 0.2 mm deep sample holder. When necessary, the samples were gently ground in a glass or agate mortar with a pestel prior to the analysis. Diffraction experiments were performed on a θ:θ vertical scan Bruker AXS D8 Advance diffractometer, equipped with a linear Lynxeye position sensitive detector, with a 300 mm goniometer radius. The radiation used was Ni-filtered Cu Kα radiation, obtained with the following generator settings: 40 kV, 40 mA. Diffraction data for phase identification were usually collected in the 5−55° 2θ range, sampling at 0.02°. Diffraction data for structure resolution were collected in the 5−105° 2θ range, sampling at 0.02°, in approximately 16 h in recycling mode.

2.4. Crystal Structure Determination. A general protocol, adopted in the powder diffraction structural characterization of $\mathbf{BCl_{III}}$, $\mathbf{BCl_{IV}}$, and all four **BI** phases, is here presented. Exact peak positions of the different phases were determined using standard peak search methods followed by profile fitting methods incorporated in the program TOPAS-R,[18] also used for indexing and determining approximate cell parameters for each phase. The unit cell parameters were then refined with the structureless Le Bail mode of the Rietveld method.[19] Density considerations and the analysis of systematic absences lead to space group determination and *Z*-evaluation ($Z' = 1$ in all phases). Structure solutions were carried out by employing a semirigid molecular fragment (the bupropion molecule protonated at the nitrogen atom, constructed using the molecular modeling optimization routine of ACD/ChemSketch, version 12.01), flexible about the four acyclic torsion angles of the side chain (see Chart 1). The pertinent halide ion was added as a freely floating atom. The location and orientation of the fragments were found using the simulated annealing algorithm incorporated in TOPAS-R. Each simulated annealing, typically yielding a single solution in a 6 h run (500 000 iterations), was run until a chemically and crystallographically reasonable structure solution was repeatedly found. The structural models were then refined by the Rietveld method. Figure 1 shows the final Rietveld refinement plots for all six crystal structures solved herein. In order to minimize evident preferred orientation effects, the sample of $\mathbf{BI_{III}}$ was mixed with Cab-o-sil (a medium surface fumed silica), and the XRPD trace of this physical mixture was used for the final refinement. For each XRPD data set, the background was modeled using a Chebyshev polynomial, peak profiles were described by the fundamental parameters approach,[20] and an average isotropic thermal factor was attributed to all atoms. The final structural models determined herein were deposited as CIF files within the Cambridge Crystallographic Database with the numbers 997396−997401.

Chart 1. Bupropion Ammonium Ion and Its Labelling Scheme, Represented with the Torsion Angles Used during Structure Solution and Discussed in Following Sections[a]



[a]Hydrogens are omitted for clarity.

2.4.1. Crystal Data of Form $\mathbf{BCl_{III}}$. $C_{13}H_{19}Cl_2NO$, fw = 276.22 g mol^{-1}, 298 K, λ (Å) = 1.5418, triclinic space group $P\bar{1}$, a = 7.7477(2) Å, b = 8.1124(1) Å, c = 13.1768(3) Å, α = 117.02(2)°, β = 81.34(2)°, γ = 89.00(2)°, V = 725.9 Å^3, Z = 2, ρ_{calc} =1.2637 g cm^{-1}, μ(Cu Kα) = 3.91 mm^{-1}, R_{Bragg} = 0.047.

2.4.2. Crystal Data of Form $\mathbf{BCl_{IV}}$. $C_{13}H_{19}Cl_2NO$, fw = 276.22 g mol^{-1}, 298 K, λ (Å) = 1.5418, triclinic space group $P\bar{1}$, a = 7.5154(3) Å, b = 7.8712(3) Å, c = 13.7033(6) Å, α = 88.12(3)°, β = 86.14(2)°, γ = 67.78(2)°, V = 748.9 Å^3, Z = 2, ρ_{calc} =1.2249 g cm^{-1}, μ(Cu Kα) = 3.79 mm^{-1}, R_{Bragg} = 0.027.

2.4.3. Crystal Data of Form $\mathbf{BI_I}$. $C_{13}H_{19}ClNOI$, fw = 367.66 g mol^{-1}, 298 K, λ (Å) = 1.5418, monoclinic space group $C2/c$, a = 8.5910(2) Å, b = 14.6100(3) Å, c = 25.6710(6) Å, β = 92.626(2)°, V = 3218.7 Å^3, Z = 8, ρ_{calc} =1.517 g cm^{-1}, μ(Cu Kα) = 17.11 mm^{-1}, R_{Bragg} = 0.038.

2.4.4. Crystal Data of Form $\mathbf{BI_{II}}$. $C_{13}H_{19}ClNOI$, fw = 367.66 g mol^{-1}, 298 K, λ (Å) = 1.5418, monoclinic space group $C2/c$, a = 14.6084(3) Å, b = 8.8069(2) Å, c = 27.0461(4) Å, β = 92.760(1)°, V = 3192.0 Å^3, Z = 8, ρ_{calc} =1.530 g cm^{-1}, μ(Cu Kα) = 17.26 mm^{-1}, R_{Bragg} = 0.047.

2.4.5. Crystal Data of Form $\mathbf{BI_{III}}$. $C_{13}H_{19}ClNOI$, fw = 367.66 g mol^{-1}, 298 K, λ (Å) = 1.5418, triclinic space group $P\bar{1}$, a = 7.9819(4) Å, b = 8.2163(5) Å, c = 13.7557(8) Å, α = 84.51(4)°, β = 84.75(4)°, γ = 63.07(4)°, V = 799.4 Å^3, Z = 2, ρ_{calc} =1.527 g cm^{-1}, μ(Cu Kα) = 17.24 mm^{-1}, R_{Bragg} = 0.034.

2.4.6. Crystal Data of Form $\mathbf{BI_{VI}}$. $C_{13}H_{19}ClNOI$, fw = 367.66 g mol^{-1}, 298 K, λ (Å) = 1.5418, monoclinic space group $P2_1/n$, a = 8.2634(5) Å, b = 9.7799(3) Å, c = 20.2113(6) Å, β = 99.98(3)°, V = 1608.7 Å^3, Z = 4, ρ_{calc} =1.518 g cm^{-1}, μ(Cu Kα) = 17.12 mm^{-1}, R_{Bragg} = 0.057.

2.5. Thermal Analysis. Differential scanning calorimetric measurements were performed on a Mettler-Toledo 822e calorimeter. The samples (weighed exactly to the second decimal in the 4−8 mg range) were loaded in aluminum pans with pierced lids and heated under a flow of nitrogen (80 mL/min). Different heating programs were used depending on the aim of the analysis: identification of thermal behavior of crystalline phases was carried out by heating at 10 K min^{-1} from 303 to 523 K, while the protocols used to generate $\mathbf{BI_{III}}$, $\mathbf{BCl_{III}}$, and $\mathbf{BCl_{IV}}$ are described alongside the other crystallization experiments. Transition temperatures were determined using the onset method, that is, the temperature at which the tangent segment taken in the first inflection point of the curve crosses the baseline. When relevant, the pans were opened after the analysis, and the recrystallized solid was analyzed via XRPD.

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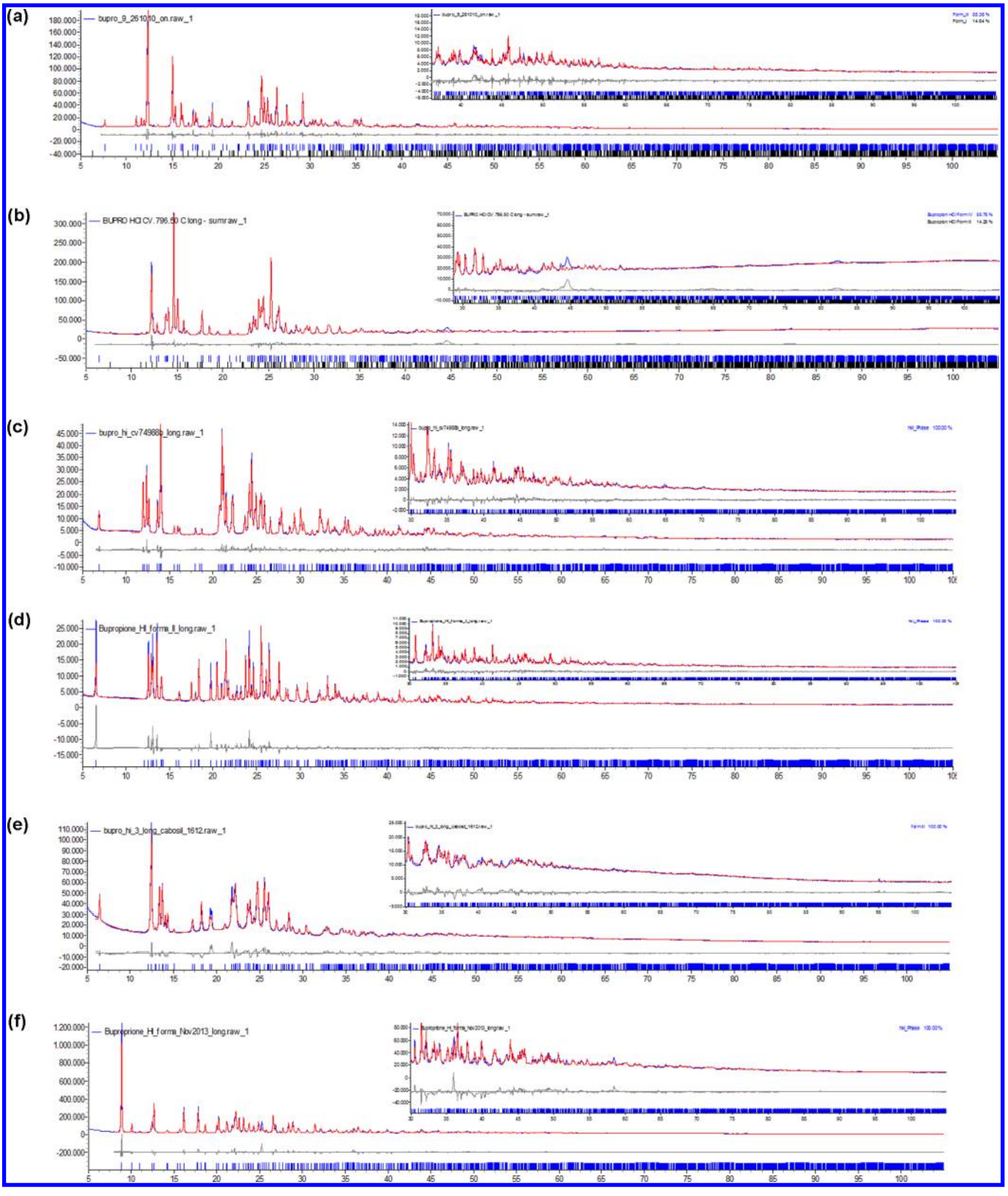

Figure 1. Final Rietveld refinement plot for (a) $\mathbf{BCl_{III}}$, (b) $\mathbf{BCl_{IV}}$, (c) $\mathbf{BI_{I}}$, (d) $\mathbf{BI_{II}}$, (e) $\mathbf{BI_{III}}$, and (f) $\mathbf{BI_{IV}}$ with difference plot and peak markers at the bottom. The insets show the high angle region, magnified 5×.

2.6. Solution NMR Analysis. The chemical identity of all phases analyzed was verified by ^{1}H and ^{13}C NMR experiments. The spectra were run on a Mercury 300 Varian spectrometer using DMSO as a solvent. Sample concentration was in the range 0.01−0.04 M. Exchange of the mobile protons with deuterated water was carried out to confirm signal attribution.

3. RESULTS AND DISCUSSION

3.1. Comparative Crystal Chemistry. As previously reported, the different salts of bupropion show structural similarities. For instance, all the previously known structures (forms $\mathbf{BCl_{I}}$, $\mathbf{BCl_{II}}$, $\mathbf{BBr_{I}}$, and $\mathbf{BBr_{II}}$) are made up of bupropion

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molecule dimers held together by hydrogen bonding between two bridging halide ions and two NH_2^+ moieties, as schematically shown in Figure 2. According to the graph set

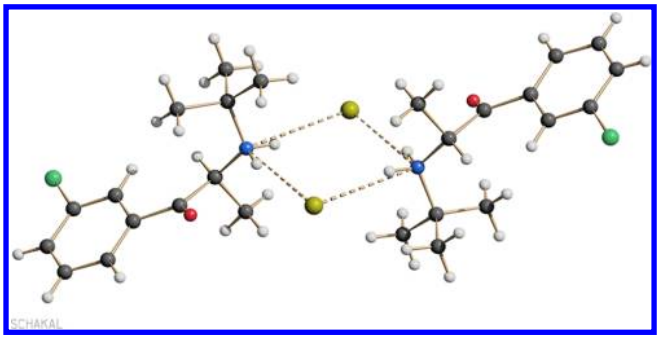

Figure 2. Supramolecular arrangement of bupropion hydrohalide dimers, highlighting the presence of H-bonded dimers of [(bupropionH)$_2$X$_2$] formulation. (Graph set notation: $R_4^2(8)$). The form depicted is **BBr$_{II}$**, which possesses an *anti* conformation.

notation,[21] this hydrogen bond motif is classified $R_4^2(8)$, because it is a ring structure made up of eight atoms and held together by four hydrogen bond donors (the hydrogen atoms covalently bonded to the nitrogen atoms) and two hydrogen bond acceptors (the halide ions). Moreover, forms **BCl$_{II}$** and **BBr$_{II}$** were reported as having similar cell parameters (shown in Table 2 alongside the cell parameters and space groups of all bupropion hydrohalide forms discussed in this paper). This suggests that the two forms may be isostructural, as confirmed by comparison of the molecular location and orientation in the crystals (see Figure S3 in the Supporting Information). Accordingly, the two forms differ only in the identity of the halide ion and, consequently, lattice parameters reflects the different sizes of the X···H (X = Cl, Br) interactions. This was an excellent starting point for our exploration of many different hydrohalide crystalline forms.

On the molecular level, the conformations of the bupropion molecules in forms **BCl$_I$**, **BCl$_{II}$**, **BBr$_I$**, and **BBr$_{II}$** seem to be very similar to one another, differing mainly in the relative orientation of the chlorine atom bound to the aromatic ring and of the carbonyl group. Specifically, **BCl$_I$** and **BBr$_I$** show the two functional groups in *syn* disposition on the outside (Figure 3), while **BCl$_{II}$** and **BBr$_{II}$** are in the *anti* disposition (as in Figure 2).

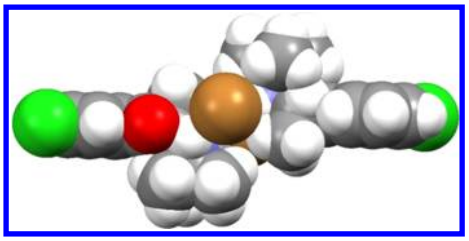

Figure 3. Space-filling model of a bupropion hydrohalide dimer, a centrosymmetric moiety present in all bupropion hydrohalide solid forms. The form depicted is **BBr$_I$**, which has a *syn* conformation.

Analogously to the previously reported structures, all the newly prepared forms of bupropion hydrochloride (**BCl$_{III}$** and **BCl$_{IV}$**) and hydroiodide (**BI$_I$**, **BI$_{II}$**, **BI$_{III}$** and **BI$_{IV}$**) here isolated are made up of dimers of bupropion molecules linked by the same $R_4^2(8)$ hydrogen bond motif between the halide ions and the ammonium groups of the two molecules. Accordingly, on the basis of ten independent characterizations, we can safely state that this is the preferred supramolecular arrangement for bupropion hydrohalide molecules, because it allows hydrophilic and charged groups to interact with one another within the dimer core, leaving the more hydrophobic and less polarized groups on the outside. All dimers are generated by crystallographic inversion symmetry, suggesting that the enantiopure salts, prepared by others[22] but not studied here, may show a different supramolecular arrangement. On the basis of these results, it is possible that in relatively concentrated solutions, bupropion hydrohalides may also exist as dimers, possibly detectable by DOSY NMR experiments. In the ^{1}H NMR experiments conducted on the different phases, however, the chemical shifts of the ammonium protons, independent of sample concentration, suggest that at the concentrations analyzed (in the range 0.03−0.08 M) and with a hydrogen bond acceptor as a solvent (d_6-DMSO), the ammonium groups interact with a single halide ion. This is demonstrated by the fact that the two ammonium protons have different chemical shifts. Moreover, the resonance frequency of one of the protons changes with the identity of the halide ion, in particular changing to higher values of chemical shift for more electronegative halides. This indicates the formation of ionic couples in solution but not the formation of the dimer structures in these conditions. This is further discussed in the Supporting Information.

Interestingly, the side chains of the bupropion molecules are arranged in very similar conformations in all phases analyzed,

Table 2. Comparative Crystal Cell Data of Different Solid Forms of Bupropion Hydrohalides[a]

form	**BCl$_I$**	**BCl$_{II}$**	**BCl$_{III}$**[b]	**BCl$_{IV}$**	**BBr$_I$**	**BBr$_{II}$**[c]	**BI$_I$**	**BI$_{II}$**	**BI$_{III}$**	**BI$_{IV}$**
ref	13	14	this work	this work	16	16	this work	this work	this work	this work
space group	$P2_1/c$	*Pbca*	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	*Pbca*	$C2/c$	$C2/c$	$P\bar{1}$	$P2_1/n$
a [Å]	14.326(2)	27.2853(5)	7.7477(2)	7.5154(3)	7.6943(8)	27.7299(9)	8.5910(2)	14.6084(3)	7.9819(4)	8.2635(5)
b [Å]	8.753(2)	8.7184(3)	8.1124(1)	7.8712(3)	7.9347(9)	8.6365(3)	14.6100(3)	8.0869(2)	8.2163(5)	9.7799(3)
c [Å]	11.885(3)	12.0422(3)	13.1768(3)	13.7033(6)	13.855(15)	12.4167(4)	25.6710(6)	27.0461(4)	13.7557(8)	20.2113(6)
α [deg]	90	90	117.02(2)	88.12(3)	85.971(3)	90	90	90	84.51(4)	90
β [deg]	78.07(2)	90	81.34(2)	86.41(2)	85.619(2)	90	92.626(2)	92.760(1)	84.75(4)	99.98(3)
γ [deg]	90	90	89.00(2)	67.78(2)	65.974(3)	90	90	90	63.07(4)	90
V [Å^3], Z	1458.2, 4	2864.7, 8	725.9, 2	748.9, 2	769.7, 2	2973.7, 8	3218.7, 8	3192.0, 8	799.4, 2	1608.6, 4
V/Z	365	358	363	374	385	371	402	399	400	402

[a]ESDs in parentheses. For an explanation of the nomenclature used for bupropion solid forms, see Table 1 [b]The cell reported is not the reduced cell. This is to make it structurally comparable with other forms, as is shown in Figure 4. [c]The values of the crystal axes were inverted compared with the values reported previously in the literature for direct comparison with form **BCl$_{II}$**.

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Table 3. Most Relevant Conformational Features of the Bupropion Molecule (a) in the Different Solid Forms of Bupropion Hydrohalides and (b) in the Conformations Calculated with Molecular Modeling Tools

Section a

form	ref	τ_1 [deg], $C_8-N_1-C_{10}-C_{Me}$	τ_2 [deg], $C_7-C_8-N_1-C_{10}$	τ_3 [deg] $C_5-C_7-C_8-N_1$	τ_4 [deg], $C_6-C_5-C_7-C_8$	class
BCl_I	13	179.0(3)	−79.9(3)	148.2(1)	−154.8(2)	*syn*
BCl_{II}	14	169.9(4)	−84.9(4)	152.3(2)	−15.0(3)	*anti*
BCl_{III}	this work	175.7(5)	−80.9(4)	147.6(2)	178.0(3)	*syn*
BCl_{IV}	this work	179.6(5)	−82.1(4)	148.4(2)	3.5(2)	*syn*
BBr_I	16	177.0(7)	−79.8(6)	149.2(5)	179.9(10)	*syn*
BBr_{II}	16	173.2(4)	−81.0(4)	148.9(3)	−19.7(4)	*anti*
BI_I	this work	166.3(8)	−82.6(6)	154.7(3)	174.6(4)	*syn*
BI_{II}	this work	176.7(8)	−77.6(7)	145.2(3)	−169.5(4)	*syn*
BI_{III}	this work	176(1)	−74(1)	148.5(5)	173.4(5)	*syn*
BI_{IV}	this work	169(1)	−78(1)	169.3(5)	−18.9(3)	*anti*

Section b

	relative energy [kcal mol^{-1}]	τ_1 [deg], $C_8-N_1-C_{10}-C_{Me}$	τ_2 [deg], $C_7-C_8-N_1-C_{10}$	τ_3 [deg] $C_5-C_7-C_8-N_1$	τ_4 [deg] $C_6-C_5-C_7-C_8$	class
most stable	0	163.2	−175.6	152.9	1.2	*anti*
most stable *syn*	+0.23	163.3	−175.8	152.7	−178.8	*syn*
restraint on τ_2	+3.83	172.3	−80	146.9	177.8	*syn*

the observed values being summarized in Table 3a. As expected, the most variable conformational descriptor in the different forms is τ_4, addressing the *syn* ($C_6-C_5-C_7-C_8$ torsion near 180°) or *anti* (near 0°) disposition of the Cl−Ar and CO residues.

The fact that all crystalline forms so far isolated contain the bupropion molecule in very similar conformation suggests that the adopted stereochemistry is energetically very favored. In order to verify this, molecular mechanics optimizations were performed for bupropion molecules in the gas phase.[23] A conformational scan was run, yielding several local minima. The potential energy values derived using the MM3 force field for the two best (but significantly different) conformations (*syn* and *anti*, addressed by τ_4) are nearly identical (see Table 3b), the calculated energy difference between the two conformations being only 0.23 kcal mol^{-1} (τ_1, τ_2, and τ_3 differing by 0.2° or less). Noteworthy, angles τ_1 and τ_3 have values similar to those observed in the solid state. However, τ_2 (in the gas phase approaching the −175° value) is significantly different from that observed in the solid state (with absolute values falling in the narrow 74−85° range). A closer inspection shows that τ_2 is responsible for the orientation of the hydrogen atoms bonded to the N atom, therefore affecting the ability of the molecule to form hydrogen bonds, through two halides, with its centrosymmetric partner in the solid state. Therefore, in search for a local minimum of the potential energy hypersurface that could geometrically approach the conformations observed in the different polymorphs, in a further minimization the value of τ_2 was arbitrarily restrained to −80°. The most stable conformer obtained in this way (third row in Table 3b) closely matches the geometry of the *syn* bupropion molecules found in the solids, with an energy difference of only +3.83 kcal mol^{-1} above the absolute minimum. Obviously, this small energy difference can be easily compensated by the solid state stabilizing effects (hydrogen bond interactions above all).

The fact that all the crystalline forms presented herein not only contain the bupropion molecule in very similar conformation but also possess the very same hydrogen bond motif implies that polymorphism (in the widest sense possible, considering all the different hydrohalide salts) is generated mainly by packing (neglecting by the *syn*−*anti* dualism). This situation is not unheard of in the scientific literature[24] but is less common than other kinds of polymorphism.

The similarity of the cell axis lengths and the identity of the space group in **BCl_{III}**, **BCl_{IV}**, **BBr_I**, and **BI_{III}** may suggest the occurrence of an isostructural group. However, the marked difference in the interaxial angles between **BCl_{III}** and the other three solid forms, not recoverable by any cell transformation, suggests the occurrence of two different (triclinic) supramolecular arrangements. In fact, while in forms **BCl_{IV}**, **BBr_I**, and **BI_{III}**, the dimers are stacked in straight rows, in **BCl_{III}**, the stacks are canted in slanted rows. This is particularly evident when viewing both structures along *a*, as shown in Figure 4. Forms **BCl_{IV}**, **BBr_I**, and **BI_{III}** are therefore isostructural, differing only in the identity of the halide ion. Incidentally, all four forms contain molecules in the *syn* conformation.

Of the four hydroiodide salts, **BI_I** and **BI_{II}** have unit cell dimensions and space group symmetry different from any other form. However, they appear to be similar to one another, because they crystallize within the same space group and with similar cell constants, *though scrambled*. A more accurate analysis of the packing, however, shows significant differences. In both cases, dimers are stacked along the short axis (which represents the "height" of two stacked bupropion dimers) but, while in **BI_{II}**, the dimers are stacked vertically when viewed along the medium axis, in **BI_I**, the stacks are slanted. Moreover, when projecting the packing down the short axis, the bupropion dimers are organized in a greek key motif in **BI_I** and in straight lines in **BI_{II}**. This is clearly shown in Figure 5.

Finally, form **BI_{IV}** appears to be structurally unrelated to all other bupropion hydrohalide forms previously observed. While it is still made up of bupropion hydrohalide molecules (of the *anti* type) mutually embraced in the "usual" $R_4^2(8)$ hydrogen bond motif encountered previously, the dimers are packed in a herringbone pattern, as shown in Figure 6.

3.2. A Quick Glance on Energetics. The previously known forms of the hydrochloride salt, **BCl_I** and **BCl_{II}**, have been reported to be enantiotropically related to one another, **BCl_{II}** being more stable at low temperatures. Unfortunately, as described above, forms **BCl_{III}** and **BCl_{IV}** were obtained only in mixtures by partially controlled (to the best of our capability) desolvation of the ethanol solvate. This made it impossible to

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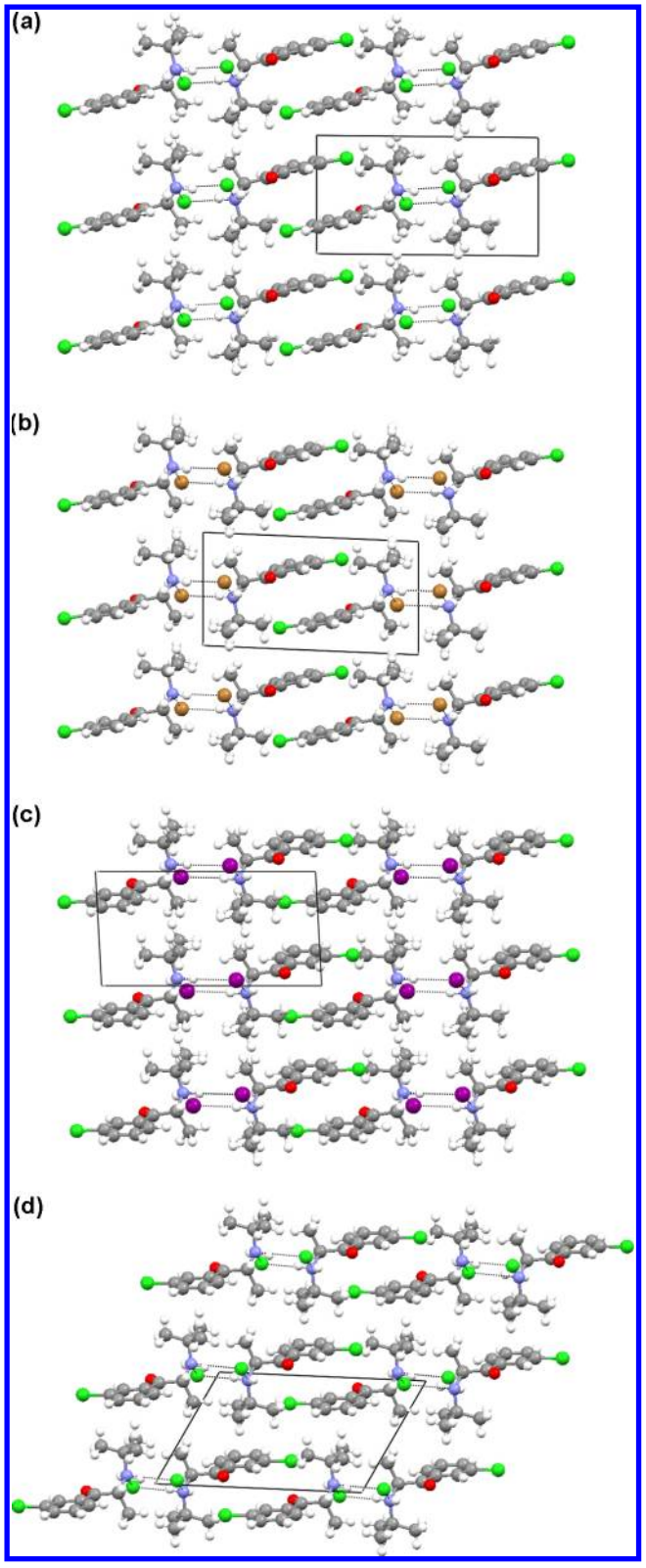


Figure 4. Comparison of the bupropion hydrohalide structures of space group $P\bar{1}$: (a) $\mathbf{BCl_{IV}}$, (b) $\mathbf{BBr_I}$, (c) $\mathbf{BI_{III}}$, and (d) $\mathbf{BCl_{III}}$.

determine the thermodynamic relationships to the known hydrochloride forms.

The thermal behavior of the two known forms of the hydrobromide salt has been discussed in the literature.[25] The endothermic conversion from $\mathbf{BBr_{II}}$ to $\mathbf{BBr_I}$ at high temperature, together with the crystal density values for the two forms (shown alongside the V/Z values of all forms in Chart 2) demonstrates that forms $\mathbf{BBr_I}$ and $\mathbf{BBr_{II}}$ are also enantiotropically related, with form $\mathbf{BBr_{II}}$ more stable at low temperatures. Interestingly, forms $\mathbf{BCl_{II}}$ and $\mathbf{BBr_{II}}$ are isostructural, both enantiotropically related to another form, and both more stable at the lower temperature. The fact that their high temperature

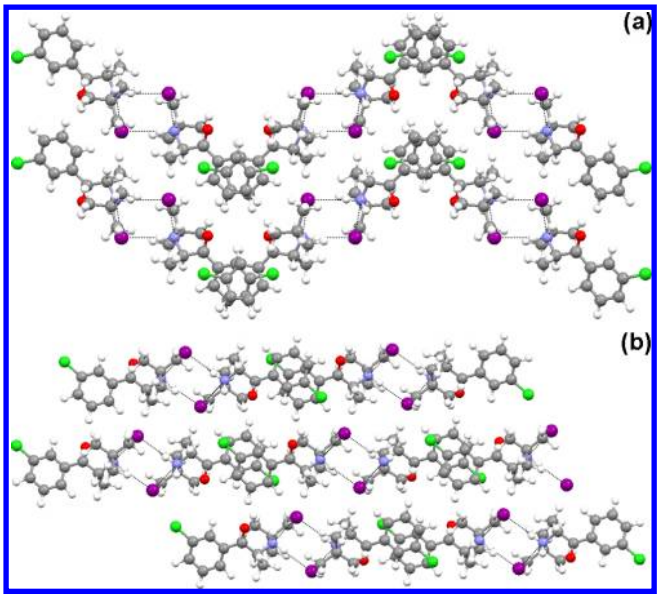


Figure 5. Crystal packing of (a) $\mathbf{BI_I}$ and (b) $\mathbf{BI_{II}}$ viewed along the short axis (*a* for $\mathbf{BI_I}$; *b* for $\mathbf{BI_{II}}$).

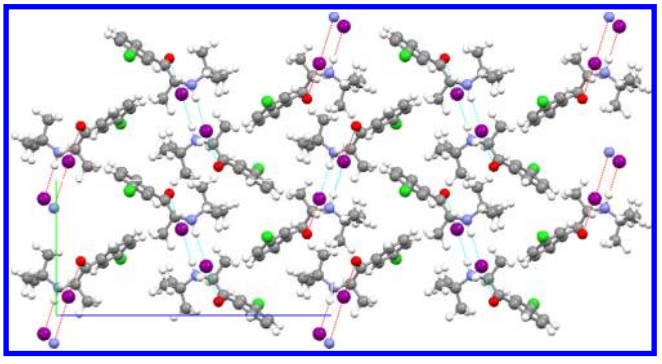
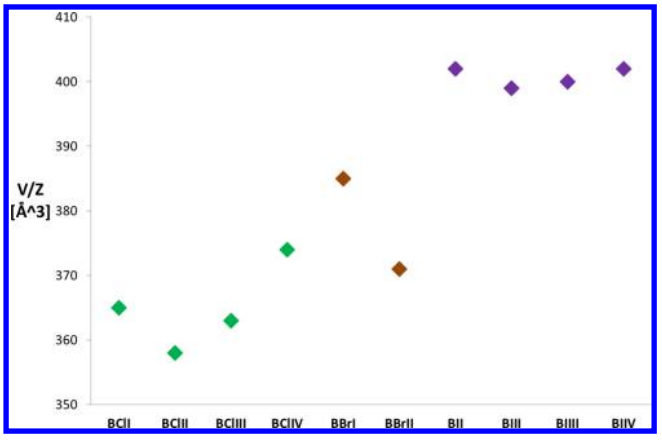


Figure 6. Crystal packing of $\mathbf{BI_{IV}}$ viewed along the *a* axis.

Chart 2. V/Z Values of Bupropion Hydrohalides



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counterparts ($\mathbf{BCl_I}$ and $\mathbf{BBr_I}$) are not isomorphous is still unexplained, and might be more than a simple curiosity.

As for the hydroiodides, the thermodynamic relationships between the different forms are not easy to unravel. Not only are the molar volumes very close for the different forms, but the DSC traces, shown in Figure S5 in the Supporting Information, offer little information. Forms $\mathbf{BI_I}$ and $\mathbf{BI_{IV}}$ show no event before the melting point (195.6 and 193.7 °C, respectively). Form $\mathbf{BI_{II}}$ melts (mp 191.9 °C) and then recrystallizes into form $\mathbf{BI_{III}}$, but this observation alone does not allow us to determine whehter they are monotropically or enantiotropically related.[26]

4. CONCLUSIONS

In this paper, we have presented the complete structural analysis of six new bupropion hydrohalide crystal phases, performed with the aid of state-of-the art *ab initio* powder diffraction methods. A full comparative crystallochemical analysis, including structural results of four additional crystal phases recently appearing in the literature (two hydrochloride and two hydrobromide salts), has been added, showing the persistency of a 2-fold embrace, in which halides are systematically hidden in a dimeric (centrosymmetric) moiety, interacting with two secondary ammonium sites. Whether this feature is maintained in enantiomerically pure forms of bupropion hydrohalides (*of no commercial use*) is not known and will be the subject of future work. More relevantly, the large diversity of different crystal packing motifs (7 for 10 different crystal phases, few of which are isomorphous) shows that even in the presence of simple molecules with limited conformational freedom, subtle modifications of the preparation conditions may selectively drive the formation of distinct phases.

Even though bupropion hydrochloride and hydrobromide salts are widely marketed for smoke cessation and SAD (seasonal affective disorder) treatments, it is highly unlikely that polymorphism will affect overall therapeutic efficiency. The extremely high solubility in aqueous media of bupropion salts, normally proposed as tablets for oral ingestion, makes any (highly justified) concern very feeble.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystal information files (CIFs) of forms $\mathbf{BCl_{III}}$, $\mathbf{BCl_{IV}}$, $\mathbf{BI_I}$, $\mathbf{BI_{II}}$, $\mathbf{BI_{III}}$, and $\mathbf{BI_{IV}}$, comparison of XRPD data present in the literature for form $\mathbf{BBr_{II}}$, final Rieveld refinement plots for forms $\mathbf{BBr_I}$ and $\mathbf{BBr_{II}}$, structural comparison of forms $\mathbf{BCl_{II}}$ and $\mathbf{BBr_{II}}$, comment on the ^{1}H NMR analyses of the phases, and DSC traces for forms $\mathbf{BI_I}$, $\mathbf{BI_{II}}$, and $\mathbf{BI_{IV}}$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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