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International Journal of Pharmaceutics 165 (1998) 107–116

international journal of pharmaceutics

Conformational analysis of Ibuprofen by crystallographic database searching and potential energy calculation

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Received 10 October 1997; received in revised form 4 December 1997; accepted 11 December 1997

Abstract

The conformational flexibility of the Ibuprofen molecule has been analysed by crystallographic database searching and potential energy calculations. The database method involves a fragment search of the Cambridge Structural Database (CSD) which identifies families of molecules with common structural fragments derived from Ibuprofen. Scatterplots of independent torsion angles defining the fragment geometries reveal structure correlations which map onto low-energy regions of the Ibuprofen potential energy surface. Thus, the preferred conformational space of the molecule is mapped out by the scatterplots, in accordance with the underlying principle of structure correlation.

Keywords: Conformational analysis; Cambridge Structural Database; MOPAC; Ibuprofen

1. Introduction

Crystal structure determination from powder diffraction data and crystal structure prediction are strategically important targets for the pharmaceutical industry. Advances in molecular modelling techniques have meant that these goals are increasingly realisable for rigid molecules (Hofmann and Lengauer, 1997). However, the problem is particularly acute for flexible drug molecules because of the complexity of the intramolecular conformational space which needs to be searched each time a trial crystal structure is created by positioning a molecule in a unit cell. The space can be reduced considerably if the search is biased towards preferred intramolecular

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0378-5173/98/$19.00
PII S0378-5173(98)00010-6

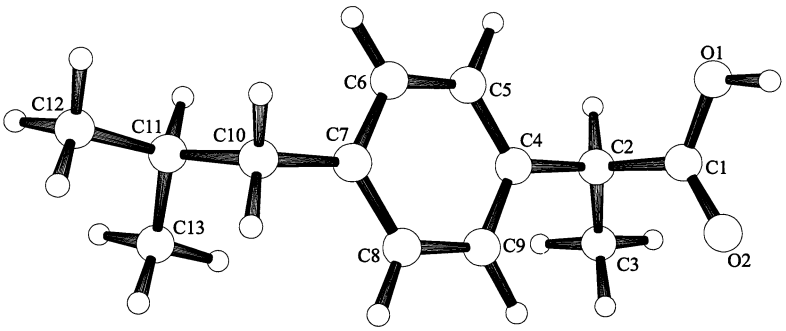


Fig. 1. An ORTEP plot (Johnson, 1971) of the Ibuprofen molecule. Atom positions were determined by single-crystal neutron refinement (Shankland et al., 1997) of the previously published X-ray racemic crystal structure (McConnell, 1974).

conformations and it is conformational analysis which concerns us here.

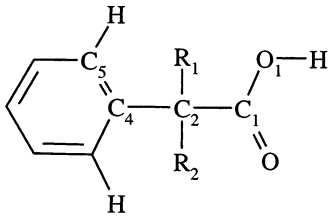
The most common approach to conformational analysis with small molecules is to use molecular mechanics, semi-empirical or ab initio methods to identify potential energy minima and energetically unfavourable conformations in isolated molecules (Leach, 1996; Doucet and Weber, 1997a).

An alternative approach is to use the Cambridge Structural Database (CSD) (Allen and Kennard, 1993) to analyse the frequency with which particular conformations are observed in crystal structures of molecules related by a common structural fragment. The wealth of crystallographic data available, coupled with the search speed and the flexibility with which output can be manipulated and visualised, makes database searching a powerful tool for conformational analysis. In line with the principle that 'observed structures tend to concentrate in low lying regions of the potential energy surface' (Bürgi and Dunitz, 1983), preferred conformations of the common structural fragment are expected to appear with greater frequency than less favoured conformations. This principle has been substantiated in a number of studies (Murray-Rust et al., 1975; Murray-Rust, 1982; Bürgi and Dunitz, 1983; 1994a,b; Schweizer, 1994; Allen, 1996; Doucet and Weber, 1997b) and follows from the observations that: (a) structurally similar molecules have similar potential energy surfaces, at least with respect to the position of minima (Bürgi and Dunitz, 1994a); and (b) crystal packing tends to minimise total lattice potential energy, so that it is generally reasonable to expect the conformation observed in a crystal to be close to a potential energy minimum. In fact, major conformational distortions, due to crystal packing, appear to be the exception rather than the rule and it is rare to observe torsion angles with strain energies >1 kcal mol^{-1} in crystal structures (Murray-Rust, 1982; Allen, 1996).

We present here the results of a conformational analysis of the non-steroidal anti-inflammatory drug Ibuprofen (Fig. 1) by CSD searching. The success of the method in mapping out the preferred conformational space of the molecule is assessed by comparing the CSD search output with potential energy calculations on an isolated molecule of Ibuprofen.

2. CSD search and potential energy calculations

Searches on fragments of the Ibuprofen molecule were performed, viewed and analysed using software supplied with the April 1997 CSD release, which contains ca. 168000 entries. Searches were confined to organic molecules only and excluded disordered and polymeric structures, structures with R factors $>10\%$ and structures identified as being in error according to CSD criteria. Appropriate constraints were used in each of the fragment searches to ensure that only meaningful hits were included in the scatterplots and this was confirmed by manual inspection. Two independent torsion angles were



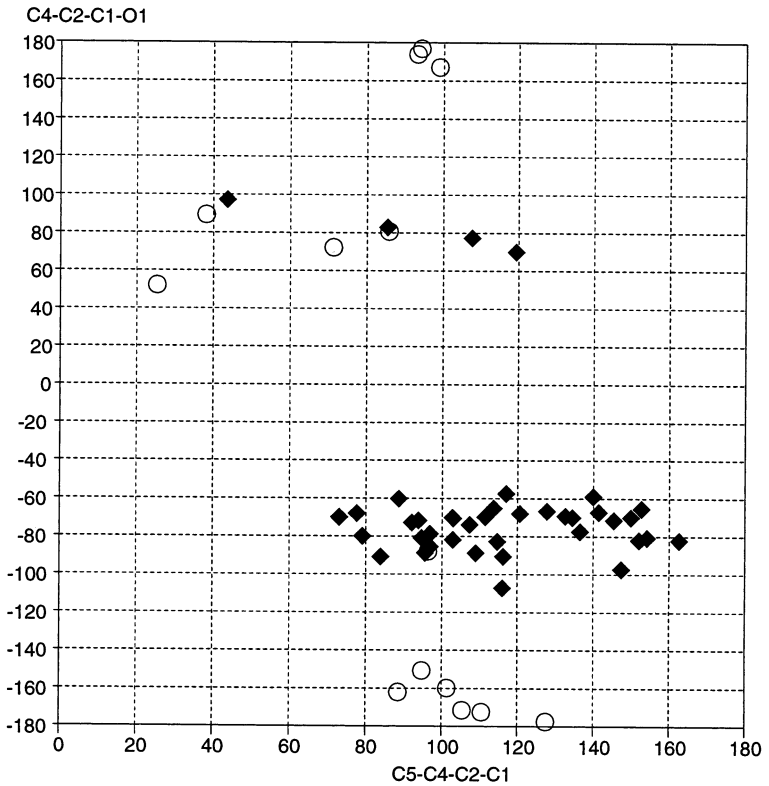
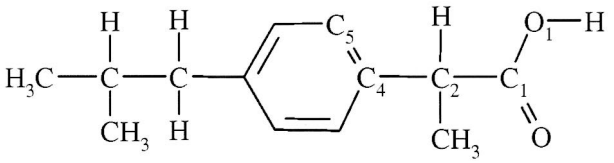


Fig. 2. A scatterplot of the C4–C2–C1–O1 and C5–C4–C2–C1 torsion angles in observed structures containing the fragment shown. The points correspond to observations which derive from compounds with R1 = H, R2 ≠ H (◆) and R1 = R2 = H (○) (observations corresponding to R1 ≠ H, R2 ≠ H not shown). C5–C4–C2–C1 was measured to the ring carbon atom which resulted in a torsion angle in the range 0° to +180°. For chiral fragments, torsion angles were measured for the enantiomer with the same relative configuration as (S)-Ibuprofen.

measured each time a specified fragment matched an entry in the database and the angles plotted as observations on a 2D scatterplot.

Potential energies were calculated for an isolated molecule of Ibuprofen using the AM1 method (Dewar et al., 1985) implemented in the program MOPAC version 5.0 (Stewart, 1990). A fully optimised molecule was input into a series of constrained optimisations in which two torsion angles were stepped through 360° at 20° intervals. The heat of formation was calculated at each step with both torsion angles fixed and all other structural parameters variable and internal coordinate derivatives were checked to



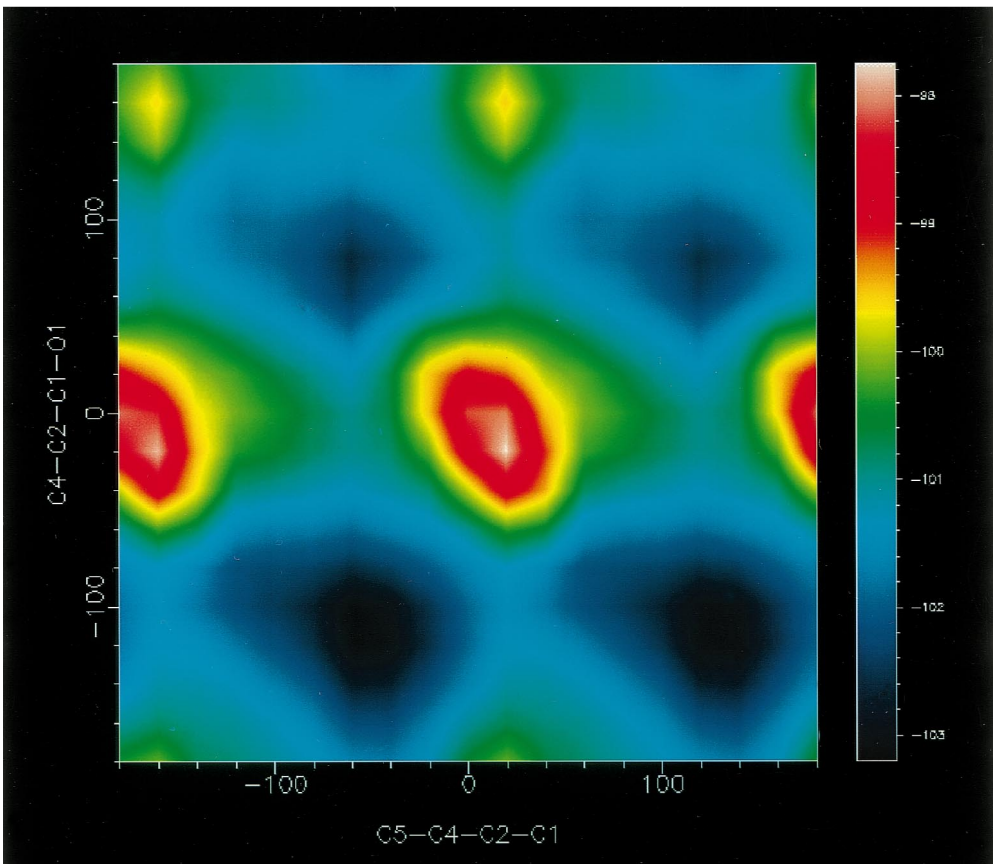


Fig. 3. Potential energy contour plot for an isolated molecule of the (S)-enantiomer of Ibuprofen. The units of energy are kcal mol^{-1} (1 kcal $mol^{-1} = 4.187$ kJ mol^{-1}).

confirm satisfactory optimisation. The results were output as 2D potential energy contour plots for direct comparison with the CSD scatterplots. Torsion angles quoted hereafter as $(x°, y°)$ refer to the horizontal and vertical axes of a contour plot or scatterplot, respectively.

3. Results and discussion

3.1. Flexibility around C1–C2 and C2–C4

A total of 60 observations from 45 different compounds were obtained for the fragment spe-

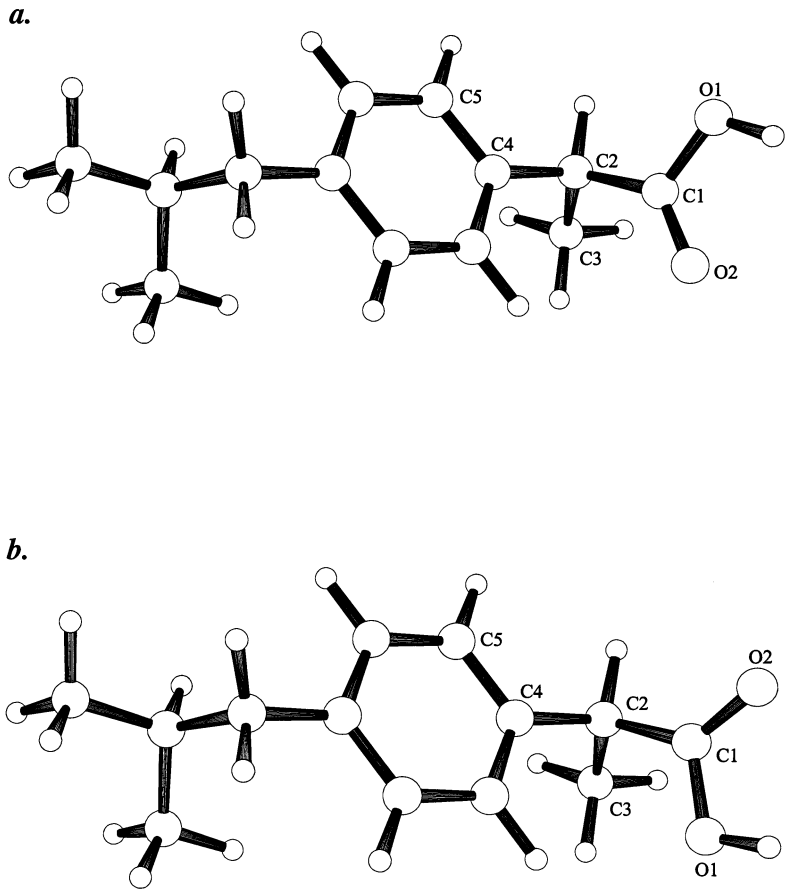
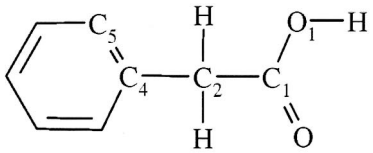


Fig. 4. A fully optimised molecule of Ibuprofen: (a) at the primary energy minimum, ca. (+ 125°, − 100°) in Fig. 3; (b) at the secondary energy minimum, ca. (+ 125°, + 80°) in Fig. 3. The biggest differences between the conformations shown in Fig. 1 and Fig. 4a are in the values of the torsion angles C5–C4–C2–C1 (difference ≈ 34°) and C4–C2–C1–O1 (difference ≈ 23°).

cified in Fig. 2. An extended search for esters of this fragment returned many more observations, with torsion angles distributed in much the same way as shown in Fig. 2. However, only the carboxylic acid fragments are discussed further here. The main subset (40 observations) derives from compounds with R1 = H, R2 ≠ H, principally R2 = –CH_3 (16 observations) and R2 = –OH (14 observations) and includes Ibuprofen in its racemic and enantiomeric crystal forms. The remaining observations derive from compounds with either R1 = R2 = H (14 observations) or R1 ≠ H, R2 ≠ H (6 observations).

The majority of the scatterplot observations lie in a cluster around C4–C2–C1–O1 = − 80° and, excepting the observation at ca. (+ 95°, − 90°), derive from compounds with R1 = H, R2 ≠ H. The position of this cluster is in reasonable agreement with the position of the primary energy minimum for Ibuprofen at ca. (+ 125°, − 100°) in Fig. 3. A comparison of Fig. 2 and Fig. 3 shows that the absence of scatterplot observations in the range C4–C2–C1–O1 = − 40° to + 40° is a consequence of the unfavourable potential energy in that region. In energy terms, the conformation of Ibuprofen observed in the racemic crystal structure (Fig. 1) is strained by ca. 0.6 kcal mol^{-1} compared with the primary energy minimum geometry (Fig. 4a) and by ca. 0.2 kcal mol^{-1} compared with the secondary energy mini-



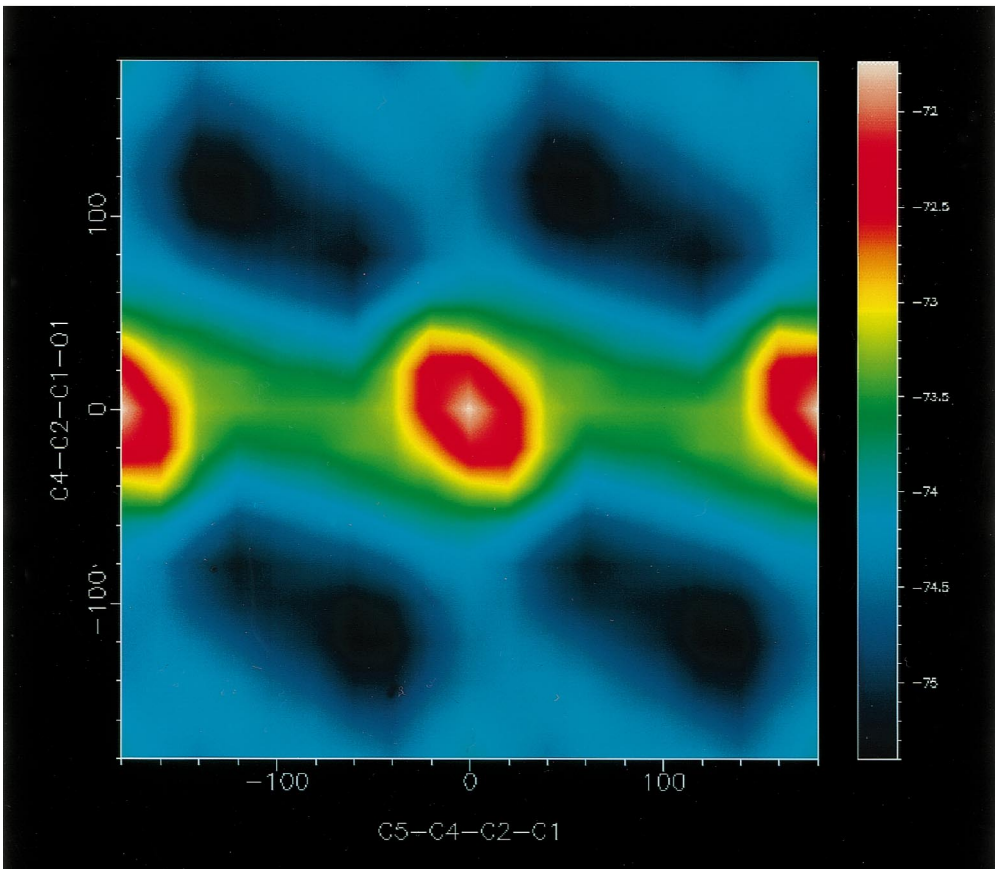
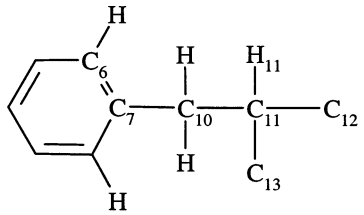


Fig. 5. A potential energy contour plot for an isolated molecule of $C_8H_8O_2$. The units of energy are kcal mol^{-1} (1 kcal $mol^{-1} = 4.187$ kJ mol^{-1}).

mum geometry (Fig. 4b). This degree of conformational distortion is consistent with what has been observed in crystal structures of other molecules (Kitaigorodsky, 1973; Murray-Rust, 1982; Allen, 1996) and is brought about by crystal packing forces.

A rotation of ca. 180° around the C1–C2 bond shown in Fig. 4a generates Fig. 4b, which corresponds to the secondary minimum at ca. (+125°, +80°) in Fig. 3, some 0.4 kcal mol^{-1} above the primary minimum. Knowing the position of this minimum, it is not surprising to find some



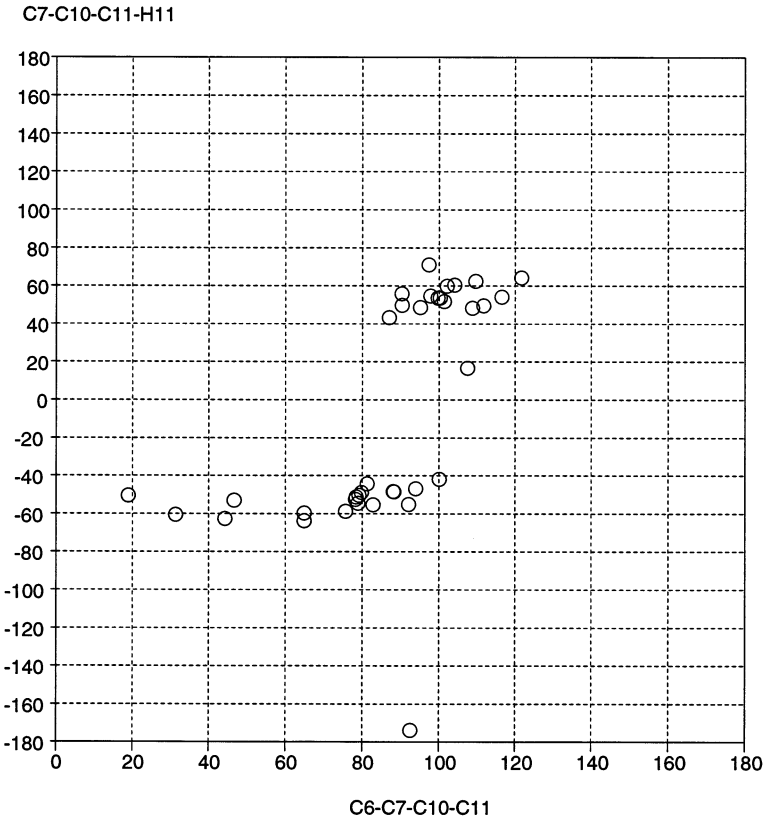
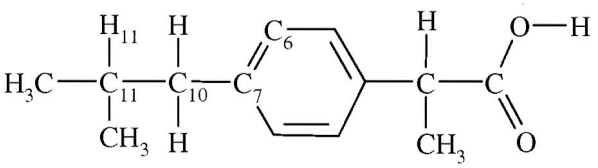


Fig. 6. A scatterplot of the C7–C10–C11–H11 and C6–C7–C10–C11 torsion angles in observed structures containing the fragment shown. C6–C7–C10–C11 was measured to the ring carbon atom which resulted in a torsion angle in the range 0° to +180°. Note that the C7–C10–C11–H11 torsion angle was selected because H11 is unique. The position of H11 in each of the observed X-ray structures does not deviate markedly from the expected tetrahedral geometry around C11 and there was therefore no need to move H11 to a standard position.

observations, albeit a relatively small number, in the corresponding region of the scatterplot. One of these, at (+85°, +85°), derives from the crystal structure of the single enantiomer of Ibuprofen, the asymmetric unit of which contains two independent molecules, with one in the region of the secondary minimum and the other in the region of the primary minimum.

The cluster of nine observations in the region C4–C2–C1–O1 = −150° to −200° in Fig. 2 maps onto relatively unfavourable areas of Fig. 3. However, the fact that these observations all



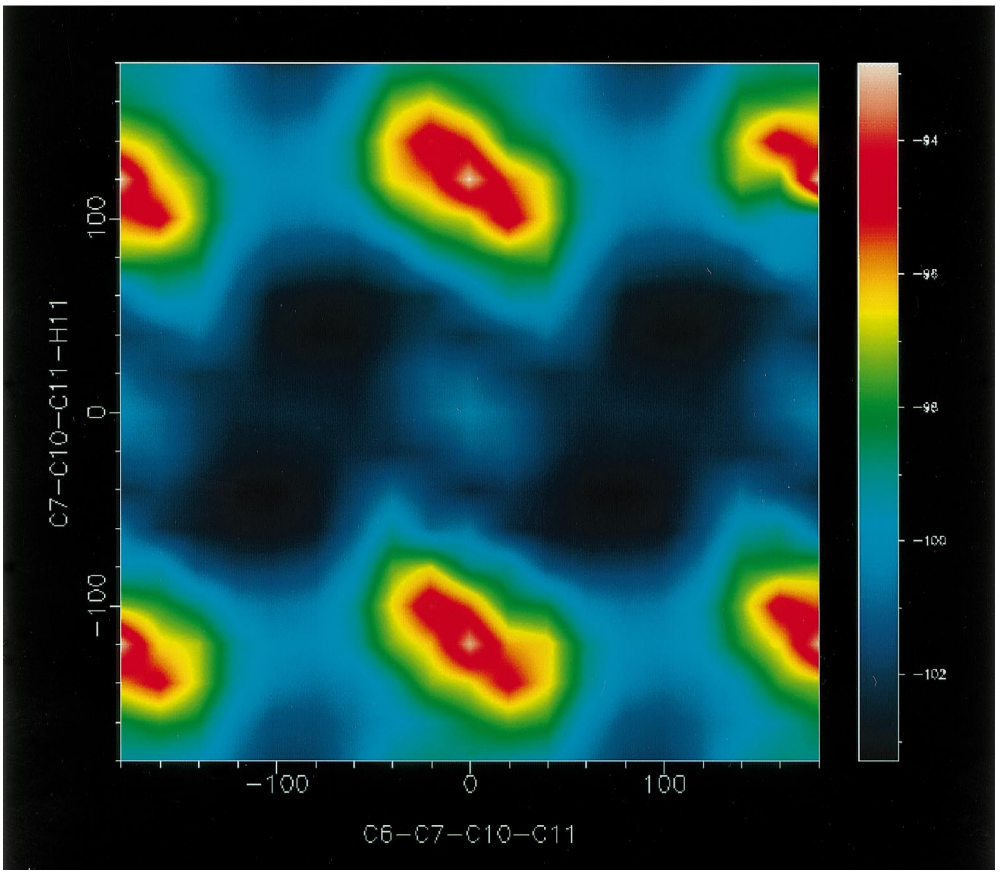


Fig. 7. A potential energy contour plot for an isolated molecule of Ibuprofen. The units of energy are kcal mol^{-1} (1 kcal $mol^{-1} = 4.187$ kJ mol^{-1}).

derive from compounds with R1 = R2 = H points to the fact that the energy surface for this fragment is somewhat different to Fig. 3 and this is confirmed in Fig. 5. The minima are broader and shallower and if we map all 14 observations for R1 = R2 = H from Fig. 2 onto Fig. 5, no observation is further than ca. 1–1.5 kcal mol^{-1} from the lowest energy point on the plot. In other words, the observations fall within relatively favourable conformational space, exactly as predicted by the scatterplot. In this context, 'favourable' means anything up to ca. 2 kcal mol^{-1} above the lowest energy point (Kitaigorodsky, 1973).

The correspondence between Fig. 2 and Fig. 3 suggests that even the strong packing influence of intermolecular hydrogen bonding (all of the hits

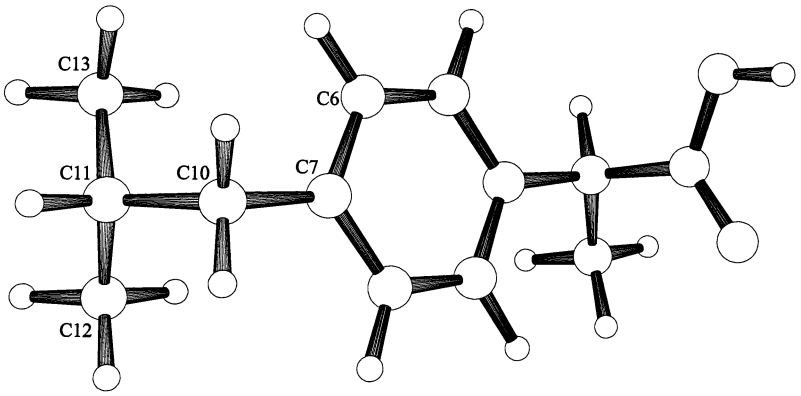


Fig. 8. A fully optimised molecule of Ibuprofen at the secondary energy minimum, ca. (+90°, 180°) in Fig. 7.

in Fig. 2 have hydrogen bonded COOH) does not displace fragment geometries significantly away from the predicted low-energy conformations for the isolated Ibuprofen molecule. It is worth underlining the fact that the most densely populated region of a scatterplot is not necessarily the lowest point on the conformational potential energy surface (Bürgi and Dunitz, 1994a), but it is certainly favourable. Therefore, if the objective is to identify favourable conformations of a specified fragment, the scatterplot helps by highlighting regions where they are likely to be found. If, as in this case, the shape of the potential energy surface is already known, the scatterplot is equally valuable because it acts as an independent means of verifying the positions of the low-lying regions.

3.2. Flexibility around C7–C10 and C10–C11

The scatterplot of 37 observations for the fragment specified in Fig. 6 has two well defined clusters, which include Ibuprofen in its racemic and enantiomeric crystal forms. The clusters correspond to conformations in which either C12 or C13 is positioned approximately *trans* to C7, which is the conformation observed for Ibuprofen in the racemic crystal structure (Fig. 1). The scatterplot clusters map onto the primary potential energy minima at ca. (+80°, −40°) and (+100°, +40°) in Fig. 7, which correspond to the *trans* conformations of Ibuprofen. The observation at ca. (+95°, −175°) in Fig. 6 coincides with the position of the secondary energy minimum in Fig. 7, which corresponds with the conformation shown in Fig. 8.

4. Conclusions

Crystal structure database searching is a powerful tool for mapping prior chemical knowledge into the problem of searching complex intramolecular conformational space. We have shown here that scatterplots of independent torsion angles defining quite general fragment geometries correlate well with regions of low potential energy in the conformational space of the Ibuprofen molecule. These findings are in accord with the principle of structure correlation (Bürgi and Dunitz, 1994a). Another paper (Shankland et al., 1998), goes on to describe how the torsion angle ranges corresponding to this preferred conformational space have been successfully used to improve the rate of convergence of a heuristic model building strategy for determining the crystal structure of Ibuprofen from X-ray powder diffraction data.

Acknowledgements

The authors thank Dr Devinderjit Sivia of Rutherford Appleton Laboratory for his contour plotting code.

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