

# The C–H...Cl hydrogen bond: does it exist?

Christer B. Aakeröy,<sup>a</sup> Timothy A. Evans<sup>b</sup>, Kenneth R. Seddon<sup>b</sup> and István Pálinkó<sup>c</sup>

<sup>a</sup> Department of Chemistry, Kansas State University, Manhattan, KS 66506-3701, USA

<sup>b</sup> School of Chemistry, The Queen's University of Belfast, Belfast, Northern Ireland, UK BT9 5AG

<sup>c</sup> Department of Organic Chemistry, József Attila University, Dóm tér 8, Szeged H-6720, Hungary

Received 5th November 1998, Accepted 30th November 1998

**The extensive occurrence of C–H...Cl hydrogen bonds has been established through a systematic statistical analysis of the Cambridge Crystallographic Database; chloride anions are shown to be better hydrogen-bond acceptor systems than neutral chloride-containing molecules, and a similar situation pertains for the other halides. As a result of this study, we propose that the conceptual van der Waals cut-off criterion be dropped for establishing the presence of weak intermolecular and intramolecular interactions, and be replaced by a distance/angle criterion determined by the empirical approach outlined here.**

The existence of C–H...X hydrogen bonding has been a matter of controversy ever since it was first proposed by Glasstone<sup>1</sup> in 1937. Donohue's categorical rejection<sup>2</sup> of such interactions has been methodically eroded through several systematic examinations of existing crystallographic information,<sup>3,4</sup> and C–H...X hydrogen bonds have been shown to be of great importance in molecular recognition processes,<sup>5</sup> the reactivity and structure of biomolecular species,<sup>6</sup> the stability of inclusion complexes,<sup>7</sup> crystal engineering,<sup>8</sup> molecular conformation<sup>9</sup> and ionic liquids.<sup>10</sup> However, elements of the chemical and biochemical community ignore, or are unaware of, such interactions, or, more dangerously, dismiss them as insignificant, as exemplified in the recent paper by Kool and coworkers.<sup>11,12</sup>

It is common practice to attempt to identify C–H...X interactions on the basis of absolute geometrical cutoffs for the H...X distance ( $d_{\text{H...X}}$ ) and the C–H...X angle ( $\alpha_{\text{CH...X}}$ ). While this is apparently a logical procedure, we had reason to doubt the distance cutoff parameter normally used, the sum of the van der Waals radii, as a meaningful selection criterion. Hydrogen bonding is mainly electrostatic in origin, an attractive force which does not decrease greatly with increasing distance,<sup>13</sup> and is thus still expected to be significant well beyond the van der Waals separation. Indeed, as we will demonstrate, to use van der Waals cutoffs as a means of identifying C–H...X hydrogen bonds is a sure way to miss most of them. The additional consideration of an angle dependence with a cutoff of  $\alpha_{\text{CH...X}} > 90^\circ$  is much more satisfactory: the C–H bond must not point away from the acceptor atom.

Several authors have studied the C–H...O interaction in great detail, and this is now widely accepted.<sup>14–16</sup> Other C–H...X interactions, however, have been infrequently proposed and rarely verified. Having identified several C–H...Cl<sup>–</sup> hydrogen bonds during a re-examination of pyridinium chloride,<sup>17</sup> we proposed<sup>18</sup> that C–H...Cl hydrogen bonds might be present in a wide range of compounds containing heterocyclic aromatic systems. Desiraju believes that the C–H...Cl interaction is still questionable,<sup>15</sup> others (including Steiner<sup>19</sup> and Zefirov<sup>20</sup>) recognise its existence. We demonstrate here that the phenomenon is universal, and not restricted to any specific category of compounds.

The Cambridge Structural Database (CSD)<sup>21</sup> affords the opportunity to investigate intermolecular hydrogen-bonding statistically. Currently containing over 160 000 entries, investigations of weak attractive hydrogen-bond interactions will normally result in a data set which is large enough to permit conclusions. Firstly, in order to examine a case where there should be no intermolecular attractive interactions, the QUEST<sup>21</sup> program was used to locate all intermolecular H<sub>2</sub>C–H...H–CH<sub>2</sub> contacts for all non-aromatic, non-organometallic systems in the H...H range 1.0–6.0 Å. No restrictions were placed upon the H<sub>2</sub>C–H...H angle for the search, in contrast to the recent excellent study by Steiner and Desiraju.<sup>22</sup> The H...H and C...H distances and the C–H...H angle were recorded for all contacts with an H...H distance within the specified range, and with a crystallographic *R*-factor of 0.08 or smaller. Using a program, QUESTPLUS, specifically designed<sup>23</sup> to process the extremely large data sets obtained from the CSD, observations with a C–H...H angle < 90° were eliminated. In order to statistically correct the data for the fact that the solid angle C–H...H is smaller for linear than for bent angles, the correction introduced by Kroon and Kanters<sup>24</sup> was applied during the sorting procedure.

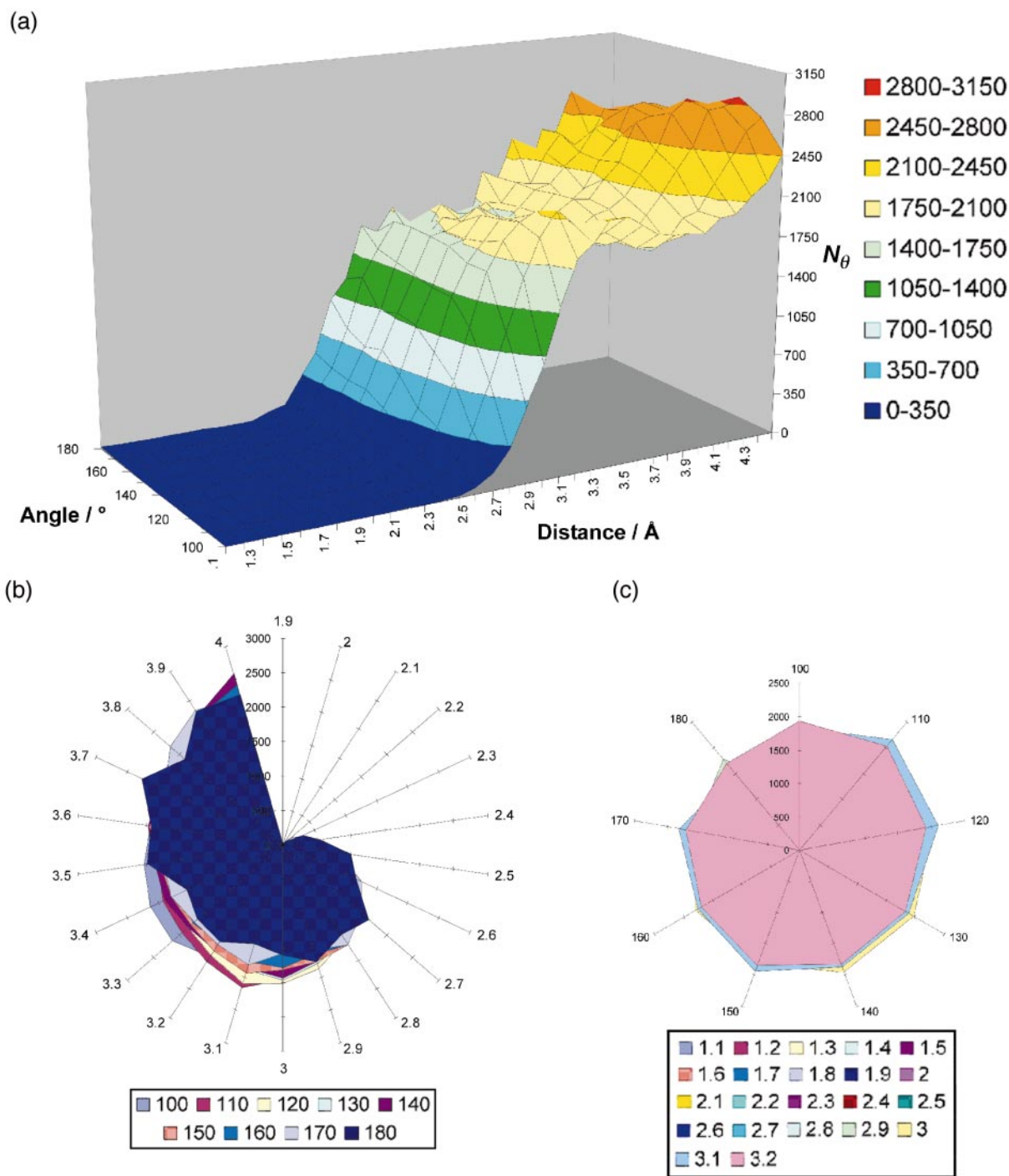
Fig. 1 shows that while C–H...H–C contacts do occur at or near the sum of the van der Waals radii (2.4 Å as determined by Pauling and Bondi<sup>25</sup>) there is no significant angular dependence displayed [Fig. 1(c)], as would be expected in the case of a specific interaction. Moreover, there is no marked maximum in the distance dependence [Fig. 1(a) and (b)].

Further searches of the CSD were performed for the following contacts, using identical parameterisation and limits (*e.g.* H...Cl range 1.0–6.0 Å): O–H...Cl, C–H...Cl<sup>–</sup>, C–H...Cl<sup>0</sup> (no ions present), C–H...Cl<sup>0</sup>–C (no ions present) and C–H...Cl<sup>0</sup>–E (E is any element other than carbon; no ions present). The data were processed as above.

Fig. 2 displays a very distinct angular and distance dependency for the traditional hydrogen-bonding case of the O–H...Cl intermolecular interaction, with the vast majority of contacts clustered across a small range at short distances, well within the sum of the van der Waals radii (3.0 Å<sup>25</sup>), and at high angles, as would be expected for such a strong hydrogen-bonding interaction.

Fig. 3 and 4 show the distribution of C–H...Cl<sup>–</sup> contacts and C–H...Cl<sup>0</sup> (for the neutral chlorine atom, where no ionic species are present) respectively. For the C–H...Cl<sup>–</sup> case, there is a marked distance dependency, displaying a maximum between 2.7 and 3.0 Å. Whilst this maximum is within the sum of the van der Waals radii of H and Cl (3.0 Å<sup>25a</sup>, 2.95 Å<sup>25b</sup>), many of the contacts lie outside this cutoff, with a well defined angular dependence [Fig. 3(a) and 3(c)]. The data in this range show a propensity towards shorter distances with more linear contacts, as would be expected with an attractive hydrogen-bonding type interaction, as in the O–H...Cl case

Letter



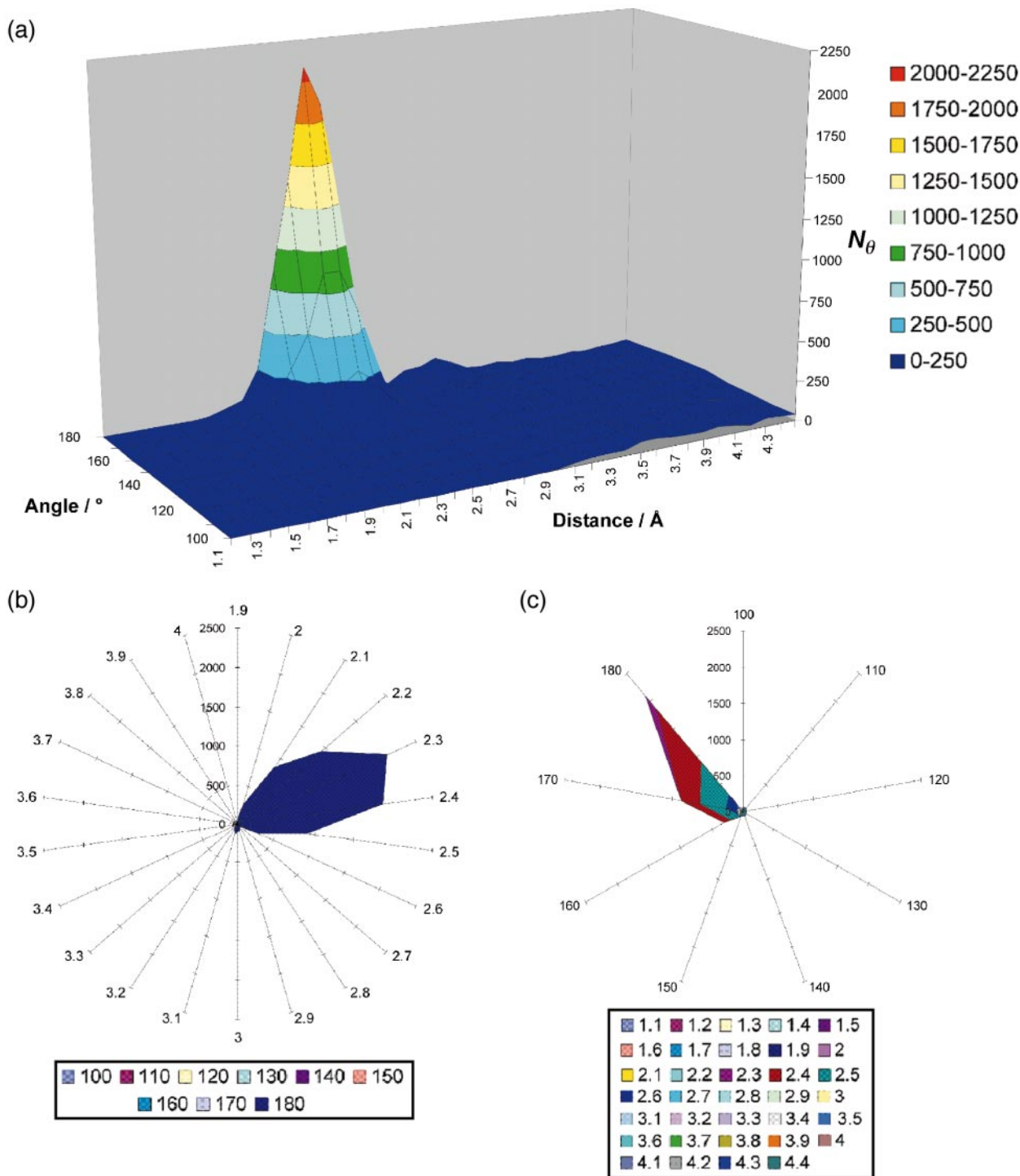
**Fig. 1** (a) Three-dimensional representation of the geometrically corrected number of hits ( $N_{\theta}$ ) as a function of C-H...H angle and H...H distance. (b) Radar representation of the number of C-H...H-C contacts as a function of distance. (c) Radar representation of the number of C-H...H-C contacts as a function of angle.

(or indeed O-H...O),<sup>26</sup> although much less pronounced (C-H being a much weaker hydrogen bond donor). This establishes the C-H...Cl<sup>-</sup> interaction to be an attractive, hydrogen-bonding interaction, commonly displayed at distances greater than the conventional van der Waal's limit.

For the case of C-H...Cl<sup>0</sup>, where no ionic species are present, the maximum is now between 2.9 and 3.1 Å and the majority of the contacts lie beyond the sum of the van der Waals radii. This maximum peak is less well defined than for the C-H...Cl<sup>-</sup> case, as the hydrogen bonds, while demonstra-

bly real, are weaker. More careful investigation of the C-H...Cl<sup>0</sup> case (no ions), shows that when Cl<sup>0</sup>-C is the acceptor group (Fig. 5) the maximum now moves outside the sum of the van der Waals radii, and its distribution is broader yet again. This suggests ever weaker hydrogen bonding. This is mirrored in a recent paper,<sup>27</sup> in which C-Cl functions are shown to be poor, but real, hydrogen bond acceptors for O-H and N-H hydrogen bond donors.

Fig. 6 demonstrates that when chlorine is bonded to atoms other than carbon (mostly metals), the maximum is found to

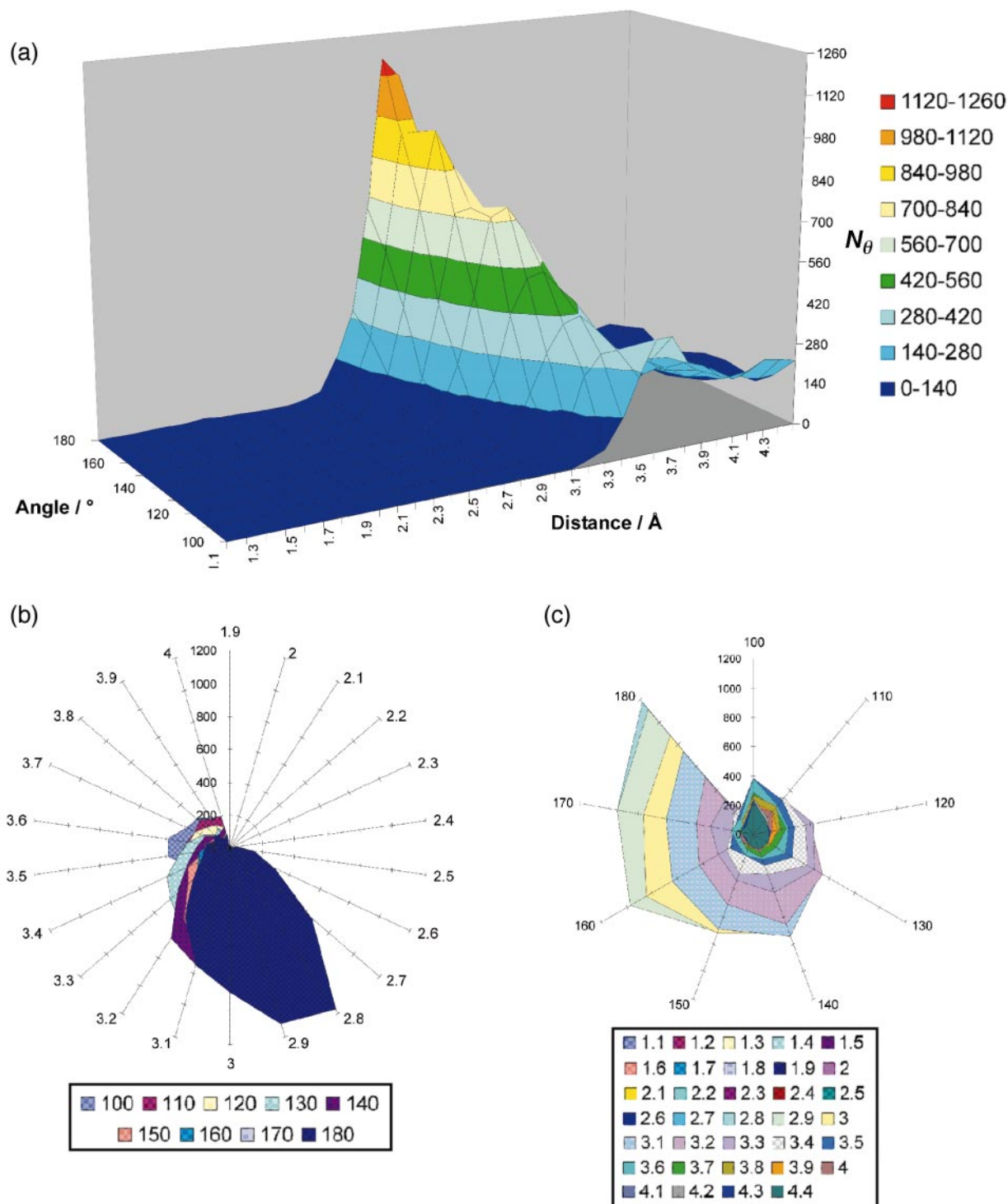


**Fig. 2** (a) Three-dimensional representation of the geometrically corrected number of hits ( $N_{\theta}$ ) as a function of O-H...Cl angle and H...Cl distance. (b) Radar representation of the number of O-H...Cl contacts as a function of distance. (c) Radar representation of the number of O-H...Cl contacts as a function of angle.

be at 3.0 Å, with the shape of the distribution more closely mirroring the C-H...Cl<sup>-</sup> case (see Fig. 3). So, for all possible cases, chlorine is behaving as a C-H hydrogen bond acceptor, but with the strength of interaction depending on the charge density on the chlorine. We find that C-H hydrogen bonds to fluorine, bromine and iodine show similar patterns of bonding to the chlorine case.

We have represented the results of the searches in three complementary graphical formats. The first, Figures (a), is a three-dimensional representation of the data, which gives an

immediate visual representation of the distribution of contacts in distance and angular space. Thus a flat angular response with a continuously rising number of hits as an irregular function of distance, *viz.* Fig. 1(a), represents an isotropic distribution of contacts. In other words, this is the non-specific interaction situation, with no identifiable hydrogen bonding. A sharp peak, *viz.* Fig. 2(a), represents a classically strong, directional hydrogen bond. Fig. 3(a)–6(a) show weaker hydrogen bonds, and the sharpness of the peak and the rate of fall off from the maximum with distance, are clear indicators of

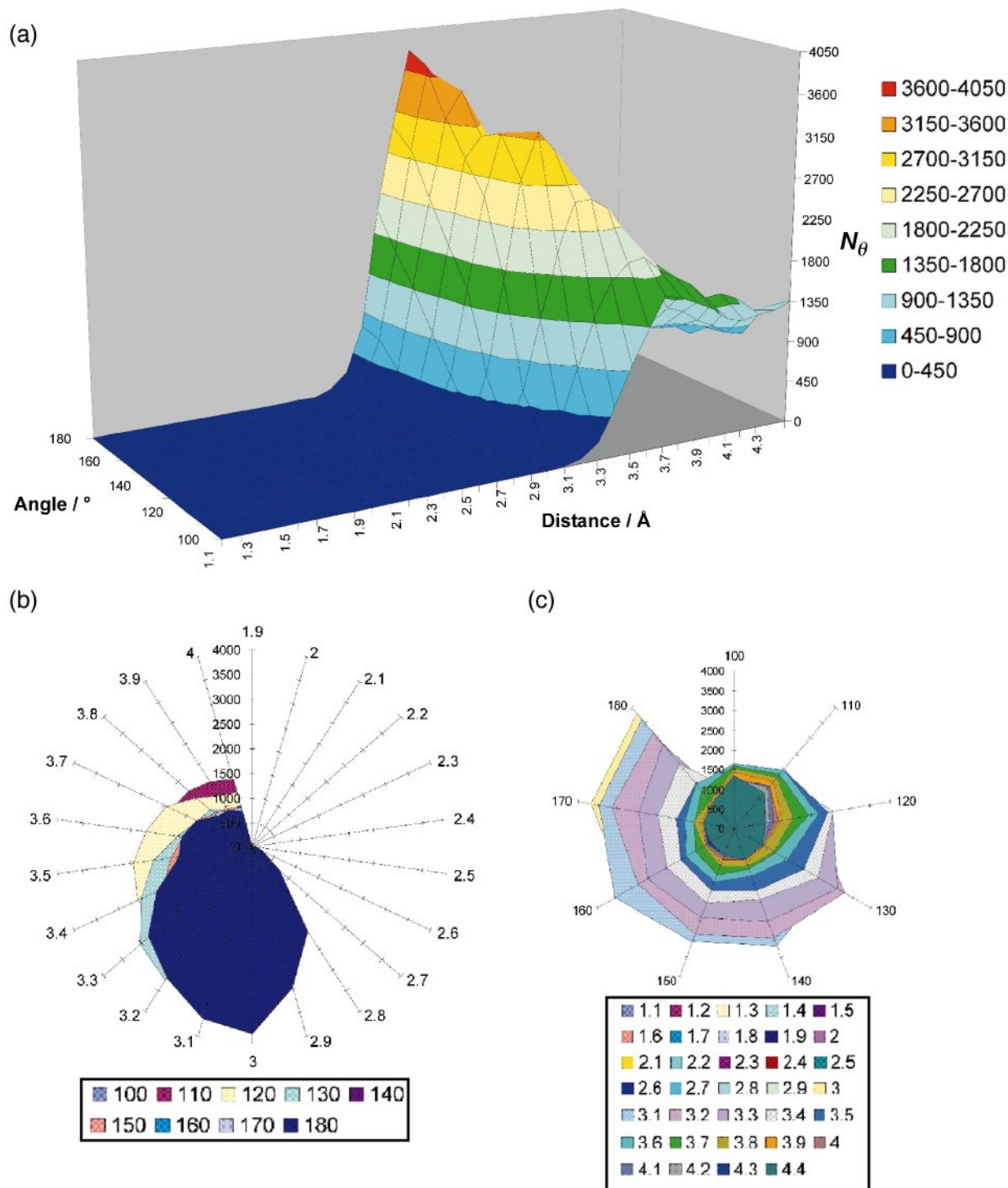


**Fig. 3** (a) Three-dimensional representation of the geometrically corrected number of hits ( $N_\theta$ ) as a function of C–H...Cl<sup>-</sup> angle and H...Cl<sup>-</sup> distance. (b) Radar representation of the number of C–H...Cl<sup>-</sup> contacts as a function of distance. (c) Radar representation of the number of C–H...Cl<sup>-</sup> contacts as a function of angle.

the strength of that interaction. Thus, this representation gives both an immediate recognition of the presence and a measure of the strength of a directional interaction. Although pedagogically useful, however, this representation is rather poor for extracting numerical information. The other two representations are radar plots: Figures (b) plot the number of contacts on a distance grid, colour-coded for angle; Figures (c) plot the number of contacts on an angular grid, colour-coded for distance. Thus, the ‘sea-shell’ in Fig. 1(b), with contacts

increasing with increasing distance, represents the non-interacting case, whereas the peaks in Fig. 2(b)–6(b) represent clearly defined interactions: the sharper the peak, the stronger the interaction. The maximum of the peak represents the most common distance encountered empirically, and the onset of the peak represents the shortest contact. In contrast, the circle in Fig. 1(c) represents an isotropic situation (the antithesis of hydrogen bonding), whereas the ‘sea-shells’ in Fig. 2(c)–6(c), all with maxima at 180°, represent the anisotropy of the inter-



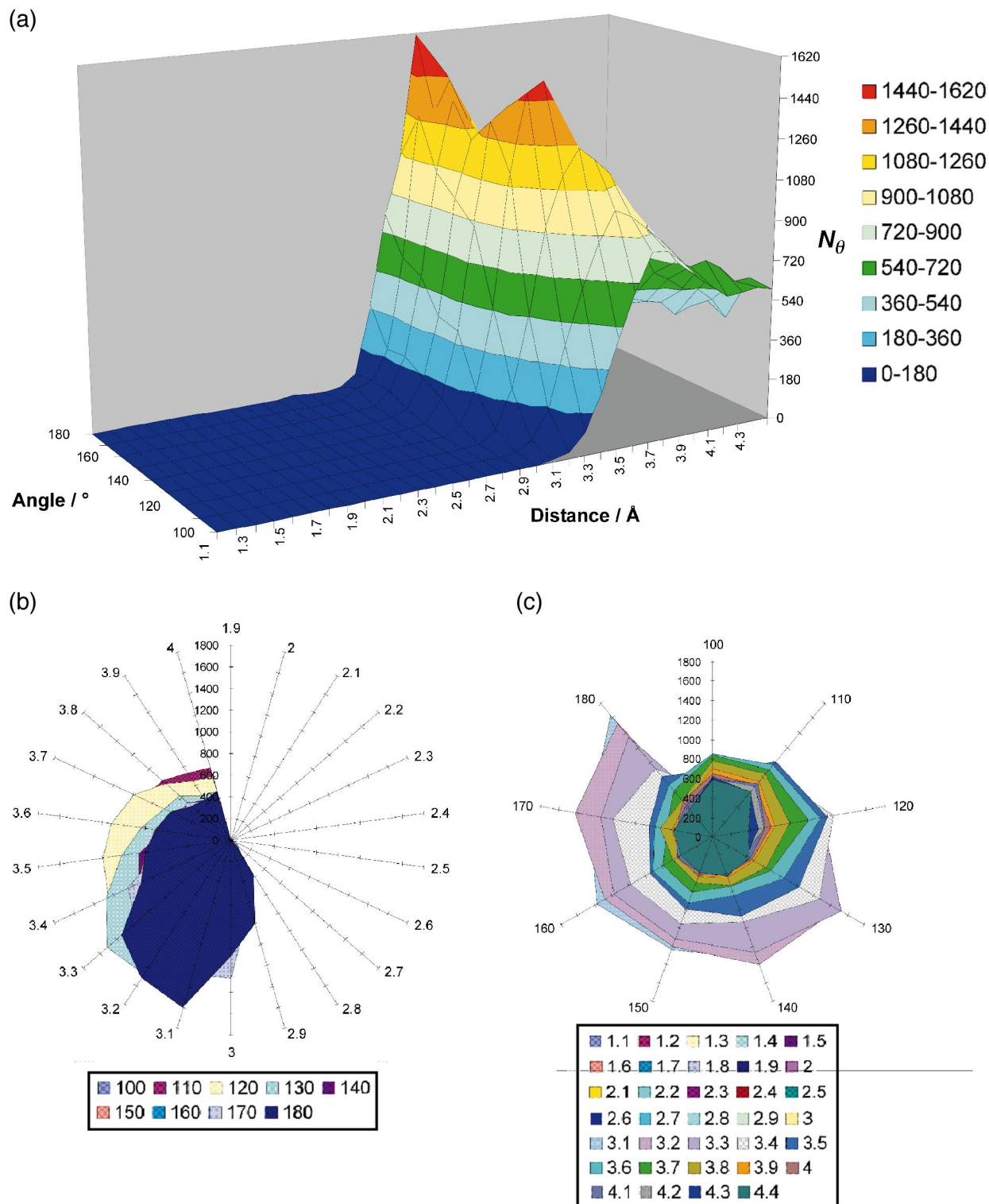


**Fig. 4** (a) Three-dimensional representation of the geometrically corrected number of hits ( $N_\theta$ ) as a function of C–H $\cdots$ Cl $^\ominus$  angle and H $\cdots$ Cl $^\ominus$  distance. (b) Radar representation of the number of C–H $\cdots$ Cl $^\ominus$  contacts as a function of distance. (c) Radar representation of the number of C–H $\cdots$ Cl $^\ominus$  contacts as a function of angle.

action. Again, the sharper the peak, the stronger the interaction. Thus, a combination of all three representations gives a very clear view of the interaction; it transforms the arbitrary traditional arguments based on van der Waals radii (a very shaky theoretical concept) to one based on experimental evidence. It also establishes a clearly quantifiable grey scale, allowing a gradual definable transition from strong angularly dependent interactions to classical dispersion forces. Moreover, the same methodology has been applied to more tradi-

tional hydrogen-bonding situations, and to X $\cdots$ X interactions (*cf.* Desiraju's seminal reports),<sup>8,28</sup> with great success.<sup>29</sup>

The investigation described in this paper demonstrates that the C–H $\cdots$ Cl hydrogen bond is a much more common phenomenon than previously thought. Many computer simulation studies do not treat C–H adequately to account properly for C–H $\cdots$ X hydrogen bonds, which can play a significant role, and we believe that the importance of such interactions to crystal engineering has been vastly underestimated. In addi-

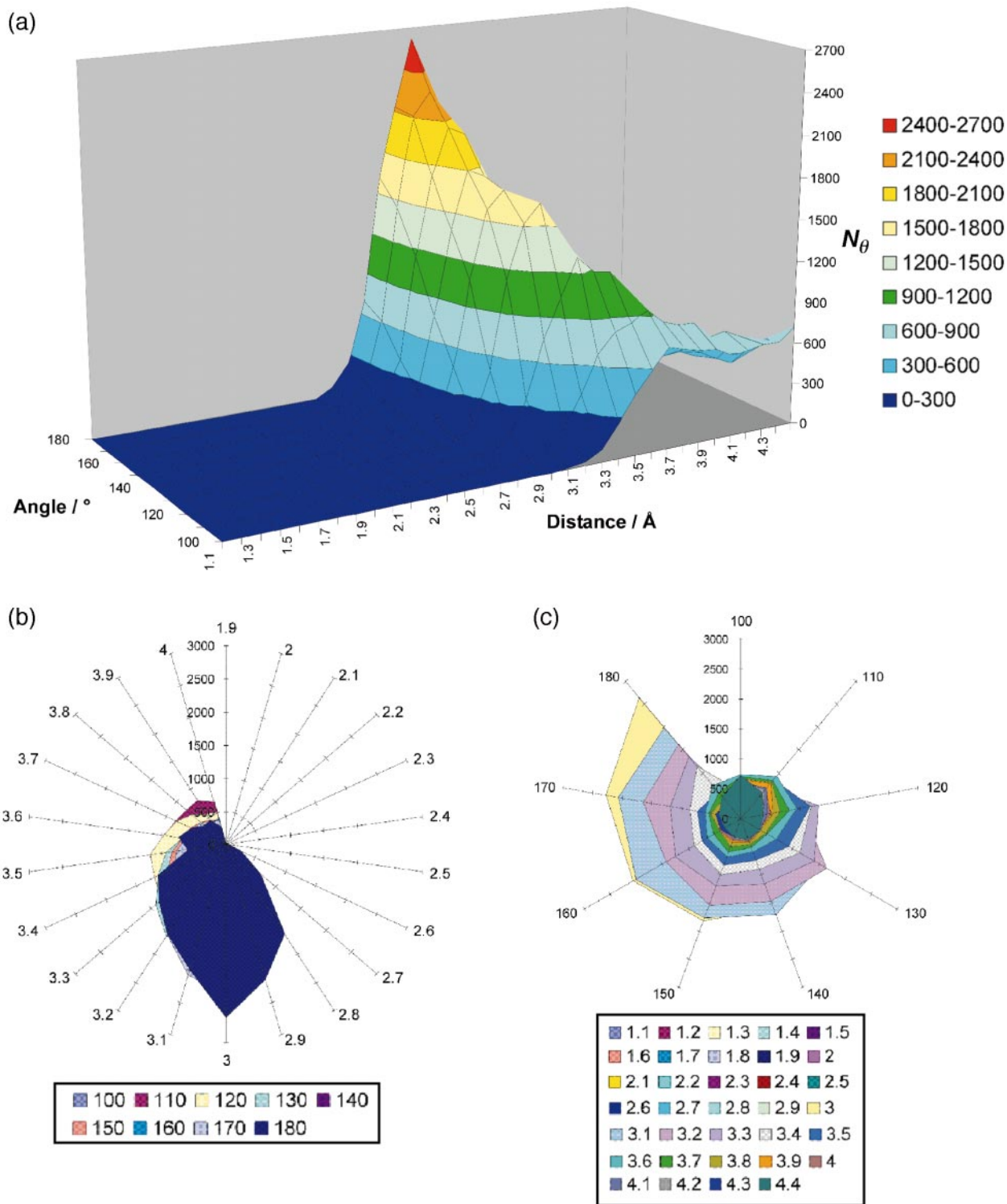


**Fig. 5** (a) Three-dimensional representation of the geometrically corrected number of hits ( $N_{\theta}$ ) as a function of C-H...Cl<sup>O</sup> angle and H...Cl<sup>O</sup> distance. (b) Radar representation of the number of C-H...Cl<sup>O</sup>-C contacts as a function of distance. (c) Radar representation of the number of C-H...Cl<sup>O</sup>-C contacts as a function of angle.

tion, it is shown that use of the sum of the van der Waals radii to validate intermolecular hydrogen-bonding interactions is a very poor criterion; an approach similar to the method used here is much more satisfactory. Indeed, we would propose that the conceptual van der Waals cut-off criterion be dropped for establishing the presence of intermolecular and intramolecular hydrogen-bonding interactions, and replaced by a distance/angle criterion determined by the empirical approach outlined here.

## Acknowledgements

We wish to acknowledge support from the EPSRC in the form of a ROPA award, the EPSRC and Royal Academy of Engineering for the award of a Clean Technology Fellowship (to K.R.S.), the National Science Foundation of Hungary (F4297/1992) and the Commission of the European Communities East-West Mobility Scheme for Scientists (to I.P.; grant 12009).



**Fig. 6** (a) Three-dimensional representation of the geometrically corrected number of hits ( $N_\theta$ ) as a function of C-H...Cl<sup>o</sup> angle and H...Cl<sup>o</sup> distance. (b) Radar representation of the number of C-H...Cl<sup>o</sup>-E contacts as a function of distance. (c) Radar representation of the number of C-H...Cl<sup>o</sup>-E contacts as a function of angle.

## Notes and references

- 1 S. Glasstone, *Trans. Faraday Soc.*, 1937, **33**, 200.
- 2 J. Donohue, in *Structural Chemistry and Molecular Biology*, ed. A. Rich and N. Davidson, W. H. Freeman, San Francisco, CA, 1968.
- 3 R. Taylor and O. Kennard, *J. Am. Chem. Soc.*, 1982, **104**, 5063.
- 4 D. Braga, F. Grepioni, K. Biradha, V. R. Pedireddi and G. R. Desiraju, *J. Am. Chem. Soc.*, 1995, **117**, 3156.
- 5 L. J. W. Shimon, M. Vaida, L. Addadi, M. Lahav and L. Leisero-witz, *J. Am. Chem. Soc.*, 1990, **112**, 6215; E. M. D. Keegstra, A. L. Spek, J. W. Zwicker and L. W. Jenneskens, *J. Chem. Soc., Chem. Commun.*, 1994, 1633; G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311.
- 6 G. A. Jeffrey and W. A. Saenger, in *Hydrogen Bonding in Biological Structures*, Springer-Verlag, Berlin, 1991; Z. S. Derewenda, U. Derewenda and P. M. Kobos, *J. Mol. Biol.*, 1994, **241**, 83; Z. S. Derewenda, L. Lee and U. Derewenda, *J. Mol. Biol.*, 1995, **252**, 248.
- 7 T. Steiner and W. Saenger, *J. Chem. Soc., Chem. Commun.*, 1995, 2087; D. Braga, F. Grepioni, J. J. Byrne and A. Wolf, *J. Chem. Soc., Chem. Commun.*, 1995, 125.
- 8 J. A. R. P. Sarma and G. R. Desiraju, *Acc. Chem. Res.*, 1986, **19**, 222.

- 9 G. Müller, M. Lutz and S. Harder, *Acta Crystallogr., Sect. B*, 1996, **52**, 1014.
- 10 A. K. Abdul-Sada, A. M. Greenway, P. B. Hitchcock, T. J. Mohammed, K. R. Seddon and J. A. Zora, *J. Chem. Soc., Chem. Commun.*, 1986, 1753; A. G. Avent, P. A. Chaloner, M. P. Day, K. R. Seddon and T. Welton, *J. Chem. Soc., Dalton Trans.*, 1994, **23**, 3405.
- 11 S. Moran, R. X.-F. Ren, S. Rumney IV and E. T. Kool, *J. Am. Chem. Soc.*, 1997, **119**, 2056.
- 12 T. A. Evans and K. R. Seddon, *Chem. Commun.*, 1997, 2023
- 13 H. Umeyama and K. Morokuma, *J. Am. Chem. Soc.*, 1977, **99**, 1316.
- 14 G. R. Desiraju, *Acc. Chem. Res.*, 1991, **24**, 290; T. Steiner and W. Saenger, *J. Am. Chem. Soc.*, 1992, **114**, 10146; T. Steiner and W. Saenger, *J. Am. Chem. Soc.*, 1993, **115**, 4540; T. Steiner, *Chem. Commun.*, 1997, 727.
- 15 G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311.
- 16 J. J. Novoa, B. Tarron, M.-H. Whangbo and J. M. Williams, *J. Chem. Phys.*, 1991, **95**, 5179; T. van Mourik and F. B. van Duijneveldt, *J. Mol. Struct. (THEOCHEM)*, 1995, **341**, 63.
- 17 K. Hensen, P. Pullmann and J. W. Bats, *Z. Anorg. Allg. Chem.*, 1988, **556**, 62; D Mootz and J. Hocken, *Z. Naturforsch., Teil B*, 1989, **44**, 1239.
- 18 C. B. Aakeröy and K. R. Seddon, *Z. Naturforsch., Teil B*, 1993, **48**, 1023.
- 19 T. Steiner, *Acta Crystallogr., Sect. B*, 1998, **54**, 456.
- 20 Y. V. Zefirov, *Crystallogr. Rep.*, 1998, **43**, 283.
- 21 Cambridge Structural Database version 5.14 (October 1997); F. H. Allen and O. Kennard, *Chem. Des. Automat. News*, 1993, **8**, 3137.
- 22 T. Steiner and G. R. Desiraju, *Chem. Commun.*, 1998, 891.
- 23 T. A. Evans, QUESTPLUS, The Queen's University of Belfast, 1994–1998.
- 24 J. Kroon and J. A. Kanters, *Nature (London)*, 1974, **248**, 667.
- 25 (a) L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, USA, 1947; (b) A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.
- 26 H. F. J. Savage and J. L. Finney, *Nature (London)*, 1986, **322**, 717.
- 27 G. Aullón, D. Bellamy, L. Brammer, E. A. Bruton and G. Orpen, *Chem. Commun.*, 1998, 653.
- 28 G. R. Desiraju, *Crystal Engineering, The Design of Organic Solids*, Elsevier, Amsterdam, 1989.
- 29 T. A. Evans and K. R. Seddon, unpublished work.

Letter 8/09309A