Crystal Environments and Geometries of Leucine, Isoleucine, Valine, and Phenylalanine Provide Estimates of Minimum Nonbonded Contact and Preferred van der Waals Interaction Distances

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Abstract: Minimum and optimum nonbonded contact distances have been determined for nonpolar side chains of amino acids. From the Cambridge Crystallographic Data Base, 110 crystal structures containing valine, leucine, isoleucine, or phenylalanine have been analyzed. Minimum contact distances are as follows: C···C = 3.41, C···O = 3.34, C···H = 2.68, H···O = 2.48, H···H = 2.17, all ± 0.05 Å. The preferred interatomic separations are 0.3–0.5 Å higher than these. Phenyl rings show preferred orientations relative both to other rings and to oxygen atoms in their environment.

Three-dimensional models of protein structure as derived from molecular mechanical calculations[1-3] or from low-resolution X-ray diffraction studies depend on a knowledge of accurate geometries of the component amino acid residues and good estimates for acceptable or preferred nonbonded contact distances. This paper provides an analysis of bond lengths, angles, torsion angles, and nonbonded contact distances found in over 100 high-resolution crystal structures containing the bulky hydrophobic amino acids leucine (Leu), isoleucine (Ile), valine (Val), and phenylalanine (Phe).

Values for minimum allowed nonbonded contact distances in amino acids were estimated by Ramachandran[4] from the shortest nonbonded contacts found in the relevant crystal structures. This was also the approach used originally by Pauling[5] and later by Bondi[6] to determine tables of van der Waals radii. Such surveys were necessarily limited to relatively few crystal structures. The use of the Cambridge Crystallographic Data Base,[7] containing over 40 000 structures, has now made it possible to examine the intra- and intermolecular environments of large families of related compounds. We have examined those amino acids which meet two criteria. First, there are no polar groups which could complicate the analysis of nonbonded intermolecular interactions by forming hydrogen bonds. Second, the side chains are long enough to reduce the influence of the amide group on intermolecular interactions. Thus, no short nonbonded contact to a side chain atom can be an indirect consequence of a neighboring hydrogen bond, and the environment of the four side chains can be regarded as being determined primarily by van der Waals interactions.

A great deal of research effort has gone into the detailed examination of small families of related crystal structures in an attempt to determine empirical potential energy functions to describe nonbonded interatomic interactions.[8-11] Our statistical approach may therefore provide an alternative view of the nature of intermolecular interactions. There have also been a number of surveys examining the preferred conformations of amino acid side chains in protein structures,[12-14] and it is of interest to compare the geometries of the residues found in this work with those in proteins.

Procedure

The Cambridge Crystallographic Data Base[7] was used to identify all crystal structures containing the fragment X–N–C(R)–C(O)–Y where X and Y are C, H, N, or O and R corresponds to Leu, Ile, Val, or Phe (see inserts in Figure 1). Crystallographic fractional coordinates for these structures were transferred to Edinburgh University's ICL 2972 computer where the data were analyzed in the following way: (1) The list of matched fragments was screened to ensure that each side chain was only incorporated into the parameter list once. (A terminal carboxyl group, for example, gives two matches for the same structural fragment.) (2) This pruned list was used to plot frequency distributions and calculate mean values and standard deviations for all chemically equivalent bond lengths, angles, and torsion angles. (3) The frequency distributions were used to identify and remove those poorly determined crystal structures with physically unreasonable bond lengths and angles. In all cases it was found that these structures had $R > 0.09$ or showed some form of gross disorder. (4) Intermolecular contacts to side chain atoms were calculated. Fractional coordinates of the asymmetric unit and space group symmetry operators were used to generate all possible neighbors out to 4.2 Å from atoms in the side chain. A contact was determined to be genuinely intermolecular if the neighboring atom was generated by any symmetry operator except (x, y, z). This procedure prevented the problem of third and fourth bonded neighbors from dominating the analysis. The final data set of unique determinations (with number of rejections in parentheses) was as follows: Val, 28 (2); Leu, 41 (1); Ile 10 (1); Phe 31 (5).

Accuracy of X-ray Results. There are a number of effects common to most crystal structure determinations which may introduce systematic errors. In this analysis there is a shrinkage of the average bond lengths involving atoms which have a large

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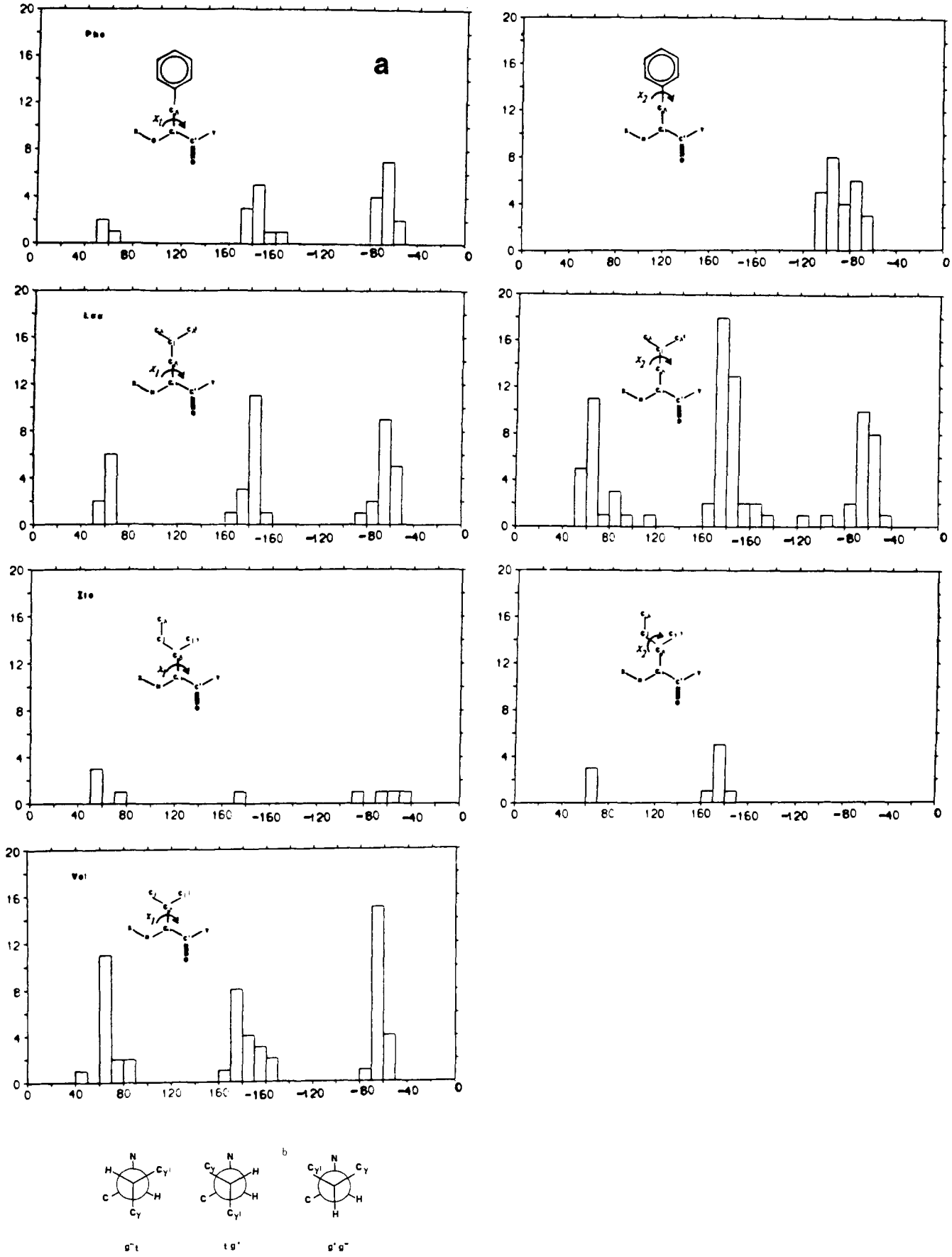

Figure 1. (a) Naming scheme for leucine (Leu), phenylalanine (Phe), isoleucine (Ile), and valine (Val). Y and X are C, H, H or O. $\chi_1 = (N\text{-}C_\alpha\text{-}C_\beta\text{-}C_\gamma)$ and $\chi_2 = (C_\alpha\text{-}C_\beta\text{-}C_\gamma\text{-}C_\delta)$. χ_1 can be unambiguously defined for Phe, Leu, and Ile. The torsion angle for Ile was defined with the methyl carbon as $C_{\gamma'}$. The histograms of χ_1 for Val (and χ_2 for Leu) show the positions for both $C_{\gamma'}$ atoms for Val (and C_δ for Leu) which lead to a doubling of these frequency distributions. The correlation of positions (g^+g^-, g^-t, tg^+) is given in Table II. For the χ_2 value of Phe, C_δ was chosen such that $-180 \leq \chi_2 < 0°$. (b) Definition of χ_1 for Val and Ile. In Val, $C_{\gamma'}$ and C_γ are chemically equivalent methyl groups. In Ile $C_{\delta'}$ = Me and C_δ = Et.

Table I. Average Bond Lengths and Angles for the Four Side Chains[a]

	Val	Leu	Ile	Phe
$N-C_\alpha$	1.469 (25)	1.480 (33)	1.484 (26)	1.460 (20)
$C_\alpha-C'$	1.524 (19)	1.522 (36)	1.525 (17)	1.523 (21)
$C_\alpha-C_\beta$	1.537 (19)	1.526 (38)	1.547 (21)	1.529 (21)
$C\beta-C_{\gamma 1}$	1.523 (15)	1.535 (33)	1.549 (19)	1.508 (19)
$C_\beta-C_{\gamma 2}$	(1.523)		1.524 (12)	
$C_\gamma-C_\delta$		1.514 (35)	1.536 (23)	1.383 (22)
$C_\delta-C_\epsilon$				1.390 (24)
$C\epsilon-C_\chi$				1.374 (28)
$N-C_\alpha-C'$	108.4 (14)	110.1 (27)	108.3 (13)	109.7 (21)
$N-C_\alpha-C_\beta$	111.3 (18)	109.5 (22)	111.9 (32)	110.4 (22)
$C'C_\alpha C_\beta$	111.4 (21)	110.5 (31)	111.5 (31)	110.7 (18)
$C_\alpha C_\beta C_{\gamma 1}$	111.0 (10)	114.6 (24)	111.0 (12)	113.2 (20)
$C_\alpha C_\beta C_{\gamma 2}$	(111.0)		110.2 (32)	
$C_{\gamma 1}C_\beta C_{\gamma 2}$	111.0 (11)		111.8 (19)	
$C\beta C_\gamma C_\delta$		111.4 (29)	113.5 (13)	120.7 (12)
$C-C-C_2$		111.4 (33)		118.7 (22)
$C-C_\delta-C_\epsilon$				120.2 (14)
$C_\delta-C_\epsilon-C_\chi$				120.2 (14)
$C_\epsilon-C-C$				119.5 (22)

[a] Estimated standard deviations were calculated from $\sigma(\bar{x}) = (\sum(\bar{x} - x_i)^2/n)^{1/2}$.

thermal motion, which is particularly evident in the shortening of bonds to terminal chain atoms. Librational corrections can be made[15] but are seldom applied. A second well known feature of X-ray crystal determinations is the shortened bond length to hydrogen because the average position for the bonding electron is displaced into the bond. In this analysis, such an effect may tend to increase the minimum intermolecular contact distance to hydrogen. In the worst possible case of a head-to-head contact, the calculated nonbonded H···H contact could be about 0.2 Å longer than the actual value.

Molecular modeling in X-ray structure refinement can also cause problems. Frequently, hydrogen atoms are input in idealized calculated positions, or phenyl rings are included as rigid idealized groups. In certain cases such a procedure can produce unreasonably short intermolecular contacts. Finally, whenever there is disorder in the structure, all intermolecular contacts must be scrutinized carefully.

Results

A summary of bond lengths and angles for the four amino acid side chains is given in Table I.

Bond Lengths. The most notable feature of the averaged bond lengths is that both Val and Ile have longer $C_\alpha-C_\beta$ bonds (1.537 and 1.547 Å) than those of Leu and Phe (1.526 and 1.529 Å). This difference is likely to be caused by intramolecular steric repulsion from the additional C_γ substituents only present in Val and Ile. The $C_\beta-C_\gamma$ bond in Val (1.523 Å) and Ile (1.524 Å) and the $C_\gamma-C_\delta$ bonds in Leu (1.514 Å) and Ile (1.536 Å) are considerably shorter than the expected sp^3-sp^3 carbon bond length. Such shrinkage involving terminal methyl groups is almost certainly an artifact caused by high thermal motion. The short $C_\beta-C_\gamma$ bond in Phe of 1.508 Å is likely to be caused by delocalization of the phenyl π electrons.

Angles. A narrowing of the $N-C_\alpha-C'$ angle in Val and Ile (108.4° and 108.3°) compared to Leu and Phe (110.1° and 109.7°) may again be explained by steric repulsion of the C_γ groups present in Val and Ile. There is a corresponding widening of the angles $N-C_\alpha-C_\beta$ in Val and Ile (111.3°, 111.9°) compared to Leu and Phe (109.5°, 110.4°). The $C'-C_\alpha-C_\beta$ shows a similar but less pronounced effect with Val and Ile (111.4°, 111.5°) and Leu and Phe (110.5°, 110.7°). Angles at methylene groups in the amino acid side chains are significantly wider than the standard tetrahedral angle of 109.4°; the average $C_\alpha-C_\beta-C_\gamma$ angles in Leu and Phe are 114.6° and 113.2°, respectively, and the average $C_\beta-C_\gamma-C_\delta$ angle in Ile is 113.5°.

It is likely that the geometry of amino acids will alter when incorporated into a constrained polypeptide chain. For example, a number of oligo-amino-isobutyric acid crystal structures[16] show a distinct and predictable distortion of angles about C_α of about 2–3° when residues form hydrogen bonded helixes.

Side Chain Conformations. The shape of the amino acid side chains is defined by two torsion angles[12] $\chi_1 = (N-C_\alpha-C_\beta-C_\gamma)$ and $\chi_2 = (C_\alpha-C_\beta-C_\gamma-C_\delta)$. Frequency distributions for the conformational angles are given in Figure 1. The idealized staggered positions are $g^+(\chi_1 = 60°)$, $t(\chi_1 = 180°)$, and $g^-(\chi_1 = -60°)$. The distributions found in this survey are compared in Table II with related work on amino acid side chain conformations found in protein structures,[12,13] and also with a theoretical study on model dipeptides.[14]

The most striking feature of the distribution of torsion angles in Figure 1 is the fact that the χ_1 and χ_2 angles are closely grouped about the ideal staggered conformations. It is also worth noting that in all four side chains the g^- conformation is favored. The next most populated conformation for Phe and Leu (both with a methylene group at C_β) is t, while Val and Ile, which have two C_γ atoms, tend to favor the g^+ conformation. A similar distribution of side chain conformation is also found in proteins.[12,13]

Earlier surveys on the conformation of aromatic amino acids[17,18] provided a similar distribution to that given for Phe in Table I, with χ_1 (g^-:t:g^+ = 45:31:23%). A similar distribution for χ_2 was also favored, with an average value near ±90°, though again individual structures can show significant deviations of ±15° from this value.

Intermolecular Interaction. The environment of each amino acid side chain was analyzed by calculating all intermolecular contacts within 4.3 Å of each side chain carbon atom and within 3.5 Å of each hydrogen atom. Frequency distributions for the different types of intermolecular C···X and H···X contacts for the side chains of Val, Leu, Ile, and Phe are shown in Figure 2.

The shortest intermolecular contacts among the Val, Ile, and Leu structures are summarized in Table III. An estimate of the lowest acceptable "distance of closest approach" (DOCA) has been made by averaging together the four shortest contacts of each type. This prevents too strong a weight being placed on any one crystal structure determination. The DOCA values are $C(sp^3)\cdots C$ = 3.57, C···O = 3.34, C···H = 2.80, H···O = 2.55, and H···H = 2.17 Å. Similarly, best estimates of a DOCA from an average of the shortest three contacts among Phe structures are C···C = 3.41 (5), C···O = 3.33 (5), C···H = 2.68 (5), H···O = 2.48 (5), H···H = 2.25 (10) Å.

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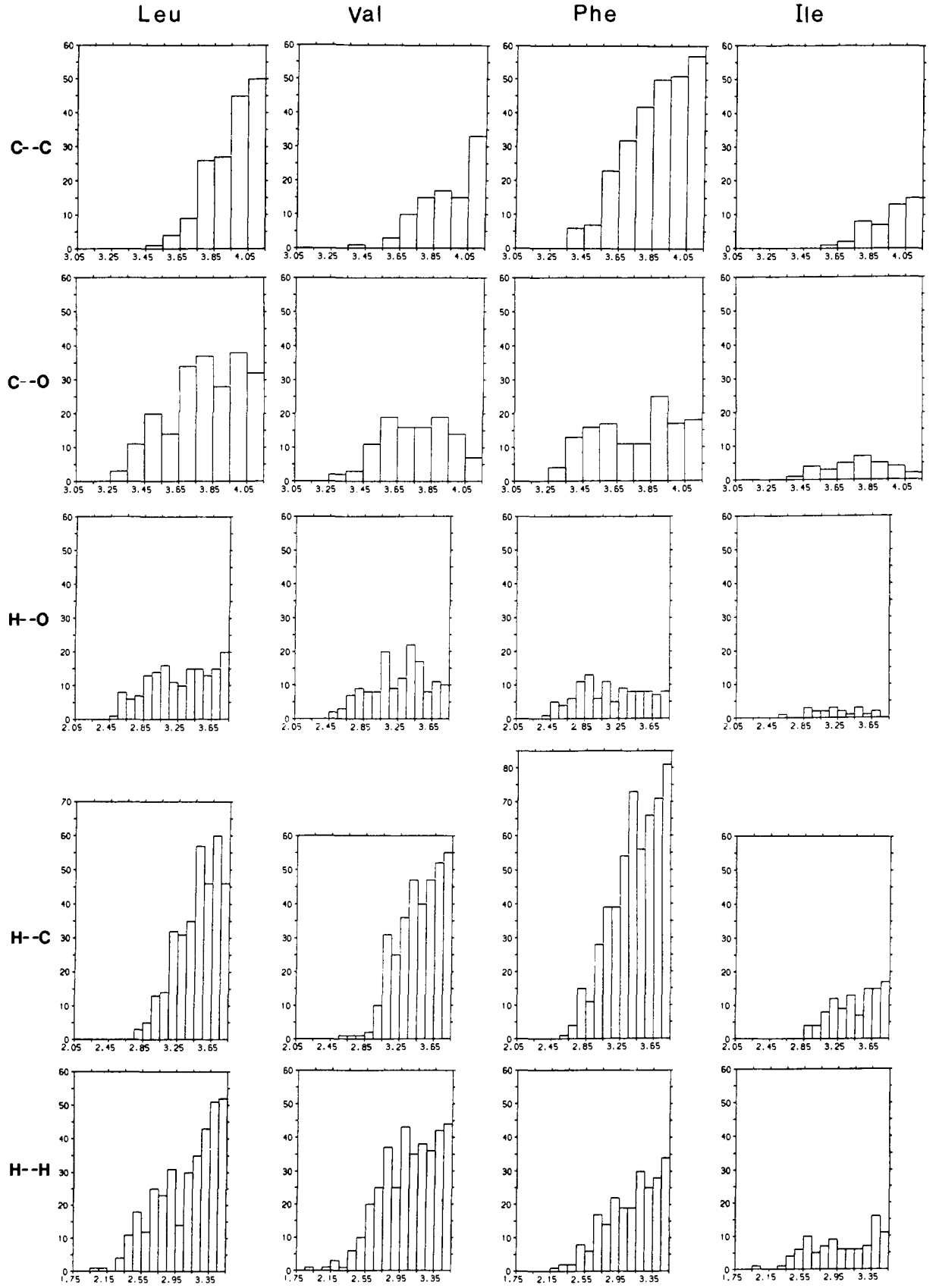

Figure 2. Frequency distribution showing the number of contacts of a given X···Y type of intermolecular interaction at a given distance between the amino acid side chain and any other C, H, O atom in the crystal environment.

As can be seen from Figure 2, the distributions do vary among these side groups. In particular, the aromatic phenyl group shows a number of differences from the aliphatic side chains. Though the minimum nonbonded distances for the four side chains all fall near the same value, the phenyl distributions involving carbon atoms are *on the average* shorter—i.e., the distributions are skewed to the left. This is as expected, as the aromatic carbon atoms are only shielded by hydrogen atoms in the plane of the ring. The O···H contacts also tend to be shorter in the aromatic systems, while the H···H contacts are on the average longer. This may

Table II. Relative Frequencies (as %) of Side Chain Conformations Found in Four Different Studies[a]

	χ_1												χ_2					
	Val			Leu			Ile			Phe			Leu			Ile		
	g^-t	tg^+	g^+g^-	g^-	t	g^+	g^-t	tg^+	g^+g^-	g^-	t	g^+	g^-t	tg^+	g^+g^-	g^-	t	g^+
Janin[13]	66	13	21	60	36	4	67	13	20	54	36	10						
Bhat[12]	45	45	10	63	31	6	65	16	18	51	40	9	46	39	15	23	73	4
Pullman[14]	43	20	37	38	26	36							37	51	12			
this work	42	27	31	41	39	20	44	12	44	50	38	12	51	44	5	0	54	22
	[11]	[7]	[8]	[17]	[16]	[8]	[4]	[1]	[4]	[13]	[10]	[3]	[4]	[18]	[2]	[0]	[7]	[2]

[a] Bhat and Janin are values from protein structure surveys.

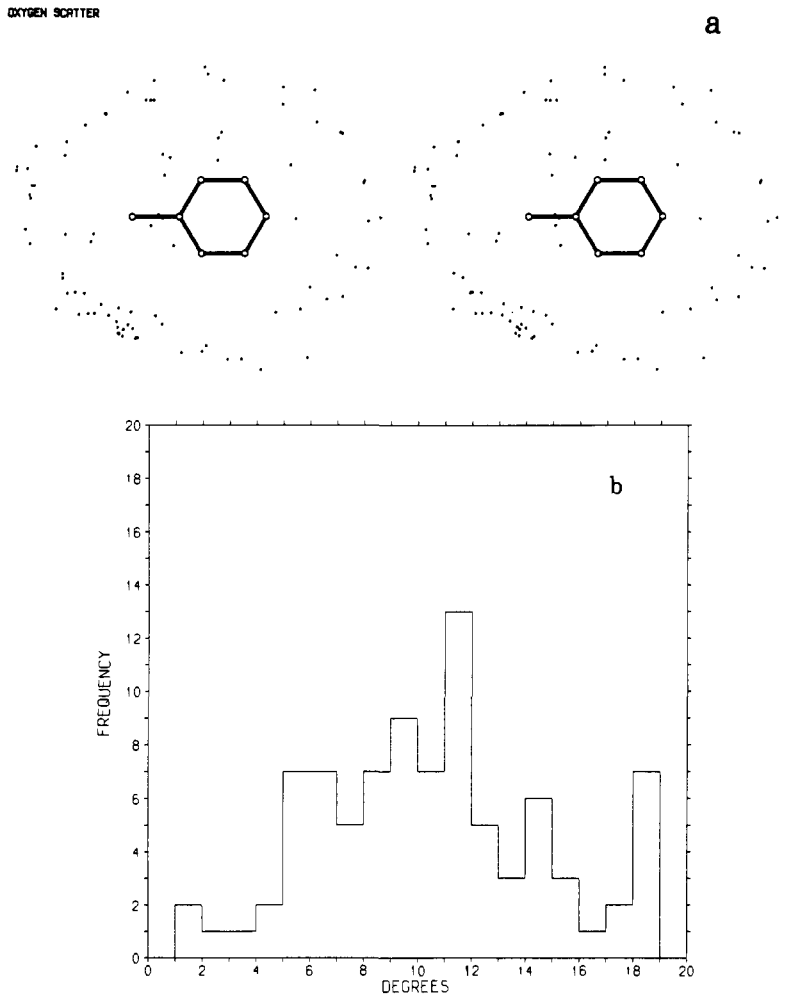

Figure 3. (a) Stereoplot showing the oxygen environment of a standard phenyl ring sitting in the *xy* plane of an orthogonal reference frame. Fractional coordinates of oxygen atoms within 4.0 Å of a phenyl carbon atom (in all 26 phenylalanine crystal structures) have been transformed to sit on this reference frame. (b) Frequency distribution of the elevation angle (E) of oxygen atoms shown in part a. The elevation angle for an oxygen atom is defined as $\tan^{-1}(x/(x^2 + y^2)^{1/2})$. Ranges of the elevation angle are taken to give approximately equal volumes.

be a result of the charge distribution in the phenyl ring which gives the hydrogen atoms a slight positive charge allowing a favorable O(δ−)···H(δ+) interaction and corresponding charge–charge repulsion between aromatic hydrogens.

Empirical van der Waals Radii. The general increase of the frequency distributions with distance in Figure 2 is consistent with the number of contacts within each shell rising proportionally with the volume of the shell. The cut-off minimum distance corresponds to the DOCA, and it is this value which has been used by both Pauling[5] and Bondi[6] as synonomous with the van der Waals distance. It is, however, likely that the preferred intermolecular contact distance, which lies at the energy minimum defined by semiempirical Lennard–Jones potential functions, will be longer than the minimum distances found in crystal structures. In many of the distributions, there are clear maxima about 0.3 Å longer than the DOCA, and it is possible that the shape of the frequency distributions reflects the relative energy of intermolecular interaction.

C···C contacts in the aliphatic group show maxima at 3.85 Å (DOCA = 3.57 Å), C···O contacts give maxima at 3.65 Å (DOCA = 3.34 Å), O···H give clear maxima at 2.90 Å (DOCA = 2.55 Å), and there are weak indications of an H···H maximum at 2.50 Å (DOCA = 2.25 Å).

The Environment of the Phenyl Group in Phenylalanine. The contact environment of each of the 26 crystallographically determined phenyl groups was transformed into a common orientation to provide an average environment of an idealized ring, Figure 3a. The environment was divided into toriodal sectors of equal volume. A frequency distribution of the angular dependence of oxygen atoms is shown in Figure 3b. It is apparent that the favored oxygen environment is in the plane of the ring, corresponding to an azimuthal angle of 0°. The apparent free energy difference (ΔG_{app}) between an oxygen lying in the plane of the ring and one lying over the face of the ring may then be calculated from $\Delta G_{app} = -RT \ln (N_f/N_e)$; where N_f = fraction of the oxygen population at a face, N_e = fraction of the oxygen

Table III. Four Shortest Intermolecular Contacts of Type X---Y Less Than a Given Cutoff Valve Found for Each of the Four Amino Acids[a]

	(Å)	val	*R* factor	Å	leu	*R* factor	Å	ile	*R* factor	Å	phe	*R* factor
C--C (≤3.70 Å)	3.424	DLVALC	6.3	3.479	GGPLMHIO	7.3	3.629	BISLEU	4.4	3.393	BAPHEEIO	9.0
	3.578	VALCAC	7.7	3.556	LPTILL	6.2				3.147	CAPHAL	10.5
	3.587	MVALHV	3.7	3.609	BCPLGYZO	8.5				3.418	PAGLAL	4.5
	3.698	MAJSUB	3.1	3.642	BCPLGYZO	8.5				3.430	AMPACCIO	4.3
	3.572			3.572						3.415		
C--O (≤3.45)	3.318	MAURTAIO	3.6	3.255	CBXLEU	10.5	3.411	LISLEU	11.7	3.270	BXCPAL	4.1
	3.332	MVALHV	3.7	3.262	BXCPLG	3.7				3.313	GPAGLM	12.6(d)
	3.419	BAKRIO	6.6	3.302	LEVARIO	8.0				3.337	CAPHAL	10.5
	3.445	BAKRIO	6.6	3.370	LEUGLYIO	11.5				3.397	ALPALIO	4.3
	3.379			3.297						3.329		
C--H (≤2.91)	2.590	MVALHV	3.7	2.788	LEUGLYIO	11.5	2.901	DAILEU	11.8	2.620	GASTRNIO	8.2
	2.739	BUFTOL	6.9	2.835	LPTILL	6.2				2.668	BOCAPR	6.7
	2.809	VALIDL	10.1	2.855	BUFTOL	6.9				2.717	BERVOJ	4.5
	2.895	BAKRIO	6.6	2.908	BACXIMIO	8.4				2.728	BERVOJ	4.5
	2.758			2.847						2.683		
O--H	2.529	BAKRIO	6.6	2.465	LEUAURIO	8.0	2.647	DAILEU	11.8	2.408	GPAGLM	12.6
	2.550	BAKRIO	6.6	2.560	DLEUHC	5.8				2.485	BIDKOO	5.3
	2.562	MVALHV	3.7	2.570	BXCPLG	3.7				2.507	APHAMA	3.9
	2.609	PRVAGL	8.4	2.586	BOFZOL	4.1				2.510	BXCPAL	4.1
	2.563			2.545						2.478		
H--H	2.112	MAURTAIO	3.6	1.974	LPTILL	6.2	1.964	DAILEU	11.8	2.193	BOCAPR	6.7
	2.151	VALIDL	10.1	2.148	LPTILL	6.2	2.263	DAILEU		2.278	TPTCMK	5.5
	2.197	BEPZAK	5.9	2.270	BUFTOL	6.9				2.290	BERVOJ	4.5
	2.166			2.176						2.216		

[a] The three columns for each side chain give the distance in Å, the unique Cambridge Crystallographic Data Base code for that structure, and the crystallographic *R* factor (%) for that determination.

population on edge. Such a calculation indicates that at 298 K the edge position is more stable by about 4.5 kJ mol^{-1}, which may again be explained by the favorable electrostatic interaction between the electronegative oxygen and the electropositive hydrogen atoms. A similar analysis of the environment of phenyl groups in protein structures[19] gives the same sort of distribution of oxygen atoms with a similar ΔG_{app} of 3.5 kJ mol^{-1}.

It is a surprising and important result to observe that, despite all the stereochemical packing constraints and larger hydrogen bonding and electrostatic energy terms, such small energy effects are consistently found in the crystal lattice.

The interaction between aromatic groups also shows a specific mode of interaction. In this analysis, any atom of a phenyl group within 4 Å of a carbon atom or 3.5 Å of a hydrogen atom of another phenyl group was regarded as an interacting group. The two phenyl groups were transformed onto a Cartesian reference frame in which one ring lies in the *xy* plane with its center at the origin and the parameters were calculated as follows: dihedral angle, the interplanar angle between the two interacting groups; $d(z)$, the distance in Å along the *z* axis between the two phenyl group centers; and $d(xy)$, the distance in Å between the centers projected onto the *xy* plane. A frequency distribution of the interplanar angles of all unique pairs of interacting phenyl groups is shown in Figure 4. There is a prominent spike in the distribution where the planes are parallel. It is very significant that for all 14 members of this group, the stacking is such that $d(z)$ lies in the narrow range 3.1 to 3.4 Å and $d(xy)$ lies in the range 3.6 to 4.3 Å. This configuration allows a mutual interaction between the hydrogen atoms of one phenyl group with the π electron cloud of the other ring. It is particularly worth noting that there are no examples of exact plate-like stacking of phenyl groups ($d(xy) = 0$). From the frequency distribution it is also apparent that the phenyl rings never give an interplanar angle in the range 5–30° presumably because any mutually favorable interactions would be destroyed. The alternative preferred geometry of interaction shows the phenyl rings to be steeply inclined to each other with mean dihedral angles of 46° and 75° which are the average values for the remaining two peaks on the distribution in Figure 4. This tilted configuration allows unhindered

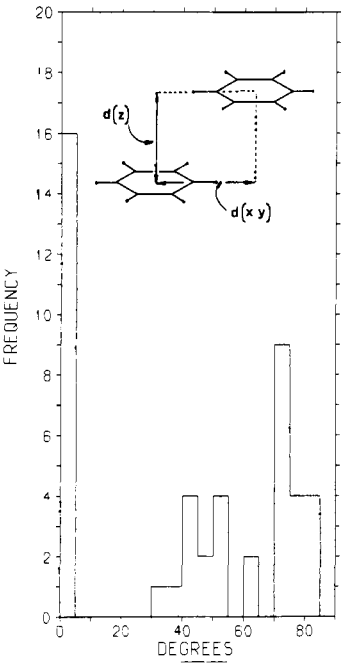

Figure 4. Frequency distribution of dihedral angles (interplanar angles) between interacting phenyl groups in phenylalanine crystal structures. The inset shows the definition of $d(z)$ and $d(xy)$, with two interacting rings drawn to show an interplanar angle of 0°.

access of the δ(+) hydrogen atoms of one group to the π cloud of the reference ring. Beevers has also shown that crystal packing in simple aromatic compounds favors a face-to-edge interaction.[20]

Theoretical studies[21,22] on the interaction of two benzene rings show that both parallel plate-stacking configuration and a theoretical energy minimum of about 11 kJ mol^{-1} at the tilted configuration ($d(xy) = 0$ and dihedral angle of 90°). On the basis

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of our statistical analysis we predict a possibly deeper minimum with the hydrogen atom slightly offset from the center of the reference ring and interacting with the π cloud above and below the C–C bonds. A second predicted energy minimum is at the parallel configuration with $d(z) = 3.3$ and $d(xy) = 4.4$ Å.

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Registry No. L-Leucine, 61-90-5; L-isoleucine, 73-32-5; L-valine, 72-18-4; L-phenylalanine, 63-91-2.

Kinetics and Mechanisms of Complex Formation of Uranyl Ion with 18-Crown-6 and Diaza-18-crown-6 Ligands in Propylene Carbonate

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Abstract: Complex formation between uranyl ion and 18C6 or diaza-18C6 ligand has been studied by stopped-flow spectrophotometric measurements, at 25 °C, in propylene carbonate ($TEAClO_4$ 0.1 M). For the experimental conditions employed the UO_2–$(18C6)^{2+}$ and UO_2–$(diaza\text{-}18C6)_2^{2+}$ complexes are entirely formed. In the presence of an excess of ligand, the kinetic process indicates three consecutive steps with the 18C6 and four observed consecutive steps with the diaza-18C6. The proposed mechanisms show the prominent role of the second and first solvation shells of the uranyl ion in the kinetic processes which can be summarized as follows: very fast formation (preequilibrium) of outer-sphere complexes with one or two ligands entering in the second solvation shell of the uranyl ion; one to four interchange steps with the loss of solvent in the inner solvation shell of UO_2^{2+} and with the formation of a metal–ligand bond.

Kinetic studies of the complexation of common crown ethers and cryptands with alkali, alkaline earth, transition, and heavy metal ions are of great interest and give models for biochemical processes. However, few investigations on the kinetic formation of these complexes have been undertaken, and the main results concern principally the alkali and alkaline earth ions complexation. The literature indicates two main mechanistic schemes for the complexation kinetics of a metal ion by a macrocyclic ligand. Nearly all of the authors propose the so-called Chock mechanism[1] for an alkali metal ion complexed by a crown ether and the more general Eigen[2] mechanism for a main group ion or a transition-metal ion complexed with a multidentate ligand. Chock's mechanism suggests that a rapid conformational preequilibrium of the ligand is followed by a reaction of the "open" form of the crown ether with the cation; the rate-determining step is the complexation step. The Eigen mechanism assumes that the formation of an outer-sphere complex between the metal and the entering ligand followed by a metal desolvation and ligand rearrangement step is the rate-determining step. As the rates of these reactions of complex formations are very fast, the kinetic measurements have been generally carried out using T jump, ultrasonic absorption, or NMR techniques. Some results are obtained in water medium,[3-9] but most in nonaqueous media.[10-24]

Only very few kinetic studies on the complexation of polyatomic units by crown ethers or cryptands have been carried out. Liesegang et al.[3] have determined the complexation rate constant of the NH_4^+ cation by the 18C6 ligand in aqueous medium. To our knowledge, there is no information available on the complexation kinetics of the uranyl ion UO_2^{2+} with any crown ether or cryptand. However, the complexation properties of that cationic unit should be of great interest because of the increasing interest in nuclear chemistry. In a preliminary study, the stability of various crown ethers and cryptands (especially of 18C6 and diaza-18C6) with uranyl ion has been investigated in propylene carbonate medium.[25,26] The 18C6 reacts with uranyl ion to give

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