The Comparative Roles of the Proton-Acceptor Properties of Amide and Carboxyl Groups in Influencing Crystal Packing Patterns: Doubly vs. Singly Hydrogen-Bonded Systems in N-Acyl Amino Acids and in Other Amide–Acid Crystals

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Abstract: Doubly vs. singly hydrogen-bonded arrangements in crystalline N-acylated amino acids R–CONH–CHR′–CO_2H are examined by energy calculations. The O(amide) is a significantly stronger proton acceptor than the O(carboxyl). Thus in one-third of the crystal structures the molecules form doubly hydrogen-bonded systems O—H···O(amide) and N—H···O(amide), despite the general preference for the maximum number of proton acceptor sites to participate in hydrogen bonds, dictated by molecular packing and conformation. The energy results are consistent with the tendency for the molecules to be interlinked via single hydrogen bonds O—H···O(amide) and N—H···O(carboxyl), rather than the reverse, and the total absence of the doubly hydrogen-bonded systems O—H···O(carboxyl) and N—H···(carboxyl).

Introduction

The packing characteristics of 16 N-acylated amino acids I have been recently classified.[1] In nine of these crystal structures each carbonyl oxygen atom of both the amide and carboxyl groups acts as a hydrogen-bond acceptor to a single (N–H or O–H) proton donor. Seven of these nine crystal structures exhibit motif **1** in which O—H···O(amide) and N—H···O(carboxyl) bonds are formed. The reverse situation, in which O—H···O(carboxyl) and N–H···O(amide) bonds are formed, as shown in motif **2**, occurs in the remaining two crystal structures.

Two crystal structures contain motif **3** in which the O—H···O(amide) bond is formed and the N–H either does not participate in a hydrogen bond, as in DL-*N*-chloroacetylalanine,[2] or is directed at a proton acceptor of the R_2 substituent which is "weak" relative to the carboxyl oxygen atom, as in *N*-formyl-L-methionine[3] and *N*-acetyl-L-cysteine.[4]

In the remaining five crystal structures the O(amide) atom participates in two hydrogen bonds while the corresponding O(carboxyl) atom does not participate in any, as shown in motif **4**. The reverse arrangement, **5**, was not observed. The motif in which the O(amide) is doubly hydrogen-bonded at the expense of O(carboxyl) is not confined to N-acylated amino acids; it was also observed in the crystal structure of *sec*-butylphthalamide[5] (II).

These results appear to be not totally in keeping with the principle that the maximum number of proton acceptor sites will participate in hydrogen bonds, recently put forward by Etter in a study on amides and carboxylic acids.[6] It is surprising that this principle does not apply more fully to the crystal structures of N-acylated amino acids, because those motifs which contain singly hydrogen-bonded systems (i.e., **1** and **2**) impose fewer constraints on both molecular packing and conformation than the doubly hydrogen-bonded motif **4**. To form the latter, it is necessary that the molecules be arranged such that both N—H···O(amide) and O—H···O(amide) hydrogen-bond distances are satisfied, that the distance between the two hydrogen atom bound to the same acceptor be not less than 2.3 Å (the minimum observed value), and that the interlinked molecules make reasonable contacts with each other. Thus there appears to be distinct advantages to the hydrogen-bonding arrangment of **4** vis-à-vis those of **1** or **2**.

These experimental results indicate that the O(amide) atom is a stronger proton acceptor than O(carboxyl). This tendency was corroborated by energy calculations in an extensive study on amides[7] and carboxylic acids,[8] where the Coulomb potential energy surfaces about the O(amide) and O(carboxyl) atoms were compared. According to the arguments presented above, we expect a general decrease in stability of the hydrogen-bonding motifs **4**, **1**, **2**, and **5**. To put this deduction on a firmer basis, we calculated the "hydrogen-bonding energies" of these motifs as they appear in their crystal structures.

Results and Discussion

The "hydrogen-bonding" energy was calculated using a 6–9 Lennard-Jones potential and an electrostatic term.[7,8] The latter included interactions between atomic monopole (i.e., atomic charges), dipole, and quadrupole moments placed at the atomic positions, derived from experimental electron density distributions according to a method proposed by Hirshfeld.[9] **6**, **7**, and **8** were used as models to represent **4**, **1**, and **2**, respectively; i.e., the acceptor molecules were modeled by formamide and formic acid and the hydrogen-bonding donor groups were represented by O–H and N–H. The donor–acceptor geometry was taken from each of the various crystal structures examined.

The hypothetical motif **5** was represented by planar models **9** and **10**, where the O—H···O=C and N—H···O=C angles (defined as θ in Table I) are 60°. In this way we estimated "hydrogen-bonding energies", neglecting other interactions which would be specific for the particular molecule and crystal structure. The results of these calculations are given in Table I together with additional relevant information on the various observed motifs. Entries 1–6 correspond to motif **1**, 7–11 correspond to motif **4**, 12 and 13 to motif **2**, and 14 and 15 to motifs **9** and **10**, respectively.

The following conclusions may be drawn from this analysis. (a) The doubly hydrogen-bonded amide **6** is more stable than the singly hydrogen-bonded **7** and **8** by the average values of 2.1 and 3.2 kcal/mol, respectively. This result is in accord with the fact that as much as one-third of the crystal structures of the N-

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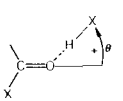
Table I. Observed and Model Hydogen-Bonding Motifs, N···O and O···O Distances D (A), θ[a] and ϕ[b] Angles (deg), and Calculated "Hydrogen-Bonding Energies" E[c] (kcal/mol)

		obsd motif	model motif	NH···O(carboxyl) D	θ	ϕ	e_1	OH···O(amide) D	θ	ϕ	e_2	NH···O(amide) D	θ	ϕ	e_3	OH···O(carboxyl) D	θ	ϕ	e_4	E
1	*N*-acetylglycine[12]	1	7	3.04	6	2	−1.8	2.56	59	1	−5.1									−6.9
2	2-chlorodibromocinnamoyl-DL-alanine[1]	1	7	3.03	13	17	−1.9	2.64	36	20	−4.9									−6.8
3	*S*-nitroso-*N*-acetyl-DL-penicillamine[13]	1	7	2.97	17	18	−1.8	2.56	55	24	−5.0									−6.8
4	*trans*-cinnamoyl-L-alanine[1]	1	7	2.93	−27	25	−0.6	2.61	−32	21	−3.4									−4.0
5	*N*-acetyl-L-tryptophan[14]	1	7	3.11	2	29	−1.5	2.58	34	45	−5.0									−6.5
6	*N*-acetyl-L-norvaline[15]	1	7	2.95	15	38	−1.5	2.55	38	5	−2.4									−3.9
7	hippuric acid[16]	4	6					2.68	−9	42	−4.7	3.01	40	53	−2.3					−6.8
8	*trans*-cinnamoyl-DL-alanine[1]	4	6					2.60	49	14	−4.8	3.04	−15	33	−4.4					−8.5
9	*N*-acetyl-L-valine[1]	4	6					2.70	−10	31	−4.9	3.02	39	35	−3.8					−8.2
10	2-chloro-*trans*-cinnamoyl-DL-alanine[1]	4	6					2.64	−14	31	−4.4	2.89	33	47	−4.3					−8.2
11	*N*-acetyl-DL-valine[1]	4	6					2.63	46	20	−3.4	3.17	−16	4	−4.9					−7.8
12	2-chloro-*trans*-cinnamoyl-L-alanine[1]	2	8									2.99	−14	4	−3.5	2.63	−59	2	−1.0	−4.5
13	dibromocinnamoyl-L-alanine[1]	2	8									2.99	2	20	−4.4	2.66	−62	19	−1.0	−5.4
14	model		9	2.94	−60	0	−1.4									2.65	60	0	−1.9	−3.3
15	model		10	2.94	60	0	−2.7									2.65	−60	0	−1.3	−4.0
	av energy values						−1.52				−4.36				−3.95				−1.3	

[a] θ is the angle between the X–H vector (X=N or O) and the C=O direction in the >C=O plane. The positive direction is shown in i. [b] ϕ is the dihedral angle between the X–H vector and the >C=O



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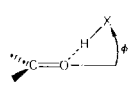
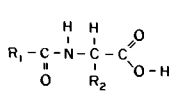


ii

plane. [c] For the singly hydrogen-bonded motifs 7 and 8 E comprises two contributions each denoted by e_i which is the energy of interaction between the proton donor and the hydrogen-bonded model molecule (formamide or formic acid). Thus for motifs 7 and 8, $E = e_1 + e_2$ and $E = e_3 + e_4$, respectively. For the doubly hydrogen-bonded motif 6, $E = e_2 + e_3$ + the interaction energy between the two donor groups (N–H and O–H) bound to the same acceptor.

Chart I



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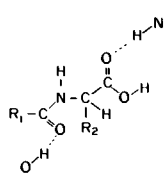

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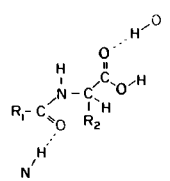

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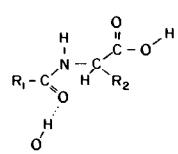

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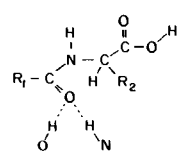

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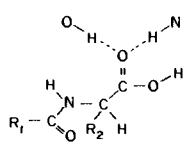

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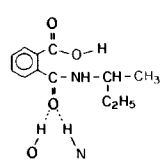

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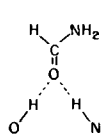

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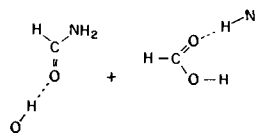

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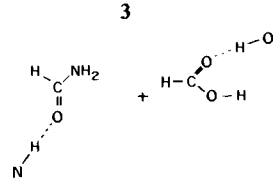

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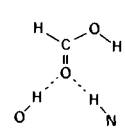

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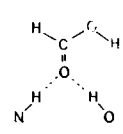

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acylated amino acids I exhibit the doubly hydrogen-bonded motif **4** despite the constraints imposed by **4** on molecular conformation and packing.

It is noteworthy that in crystal structures containing the chain-like molecules HO_2C–X–$CONH_2$ (X = CH_2CH_2, CH=CH, CH=CHCH=CH)[10] and in binary complexes between (primary and secondary) amides and carboxylic acids,[11] there is a far stronger tendency for the O(amide) to be doubly hydrogen-bonded and for the O(carboxyl) to be singly hydrogen-bonded than the reverse.

(b) Motif **7** is more stable than **8** which is in keeping with the fact that the singly hydrogen-bonded motif **1** [i.e., O—H···O(amide) and N—H···O(carboxyl)] is the most prevalent and that the singly hydrogen-bonded **2** [i.e., O—H···O(carboxyl) and N—H···O(amide)] occurs in only two of the observed crystal structures.

(c) The hydrogen-bonding energies of **9** and **10** (Table I) demonstrate why the hypothetical **5**, in which the carboxyl oxygen atom participates in two hydrogen bonds, does not occur.

(d) The average energies of the individual hydrogen-bond contributions (i.e., $\bar{e}_1$, $\bar{e}_2$, $\bar{e}_3$, $\bar{e}_4$ in Table I) reflect the observed preference for an O—H···O(amide) bond rather than the other three possibilities [i.e., OH···O(carboxyl), NH···O(amide), and NH···O(carboxyl)], in those crystal structures, represented by **3**, which contain only one active proton donor per molecule (i.e., $\bar{e}_2 < \bar{e}_4, \bar{e}_3, \bar{e}_1$). In this respect it is noteworthy that the O—H···O(amide) bond appears to be shorter, by up to 0.1 Å, than the O—H···O(carboxyl) bond. Furthermore, the O–H bond is a stronger proton donor than the N–H bond, as is evident from the O—H···O and N—H···O distances, i.e., 2.6 vs. 2.9 Å.

(e) The interaction energy between the two proton donors in the doubly hydrogen-bonded motif **6** is positive and was calculated to be about 0.4 kcal/mol; i.e., the two donor groups repel each other. Consequently, for amide or carboxylic acid molecules containing hydrogen-bonding groups of a single kind (i.e., amide or acid, but not both), the tendency should be for each acceptor oxygen atom to be singly hydrogen-bonded, which is in accord with the principle proposed by Etter.[6] On the other hand, for molecules which contain both amide and carboxyl groups, this principle is not all prevailing.

These calculations were carried out using a very simplified model which focused on the H-bonding groups in an isolated region, neglecting the residues and overall molecular packing. Nevertheless, these results are useful for the interpretation of the systematic features in a wide variety of crystal structures containing amides and carboxylic groups or a mixture thereof, as will be examined in a forthcoming paper.

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Registry No. *N*-Acetylglycine, 543-24-8; *S*-nitroso-*N*-acetyl-DL-penicillamine, 67776-06-1; *trans*-cinnamoyl-L-alanine, 84064-15-3; *N*-acetyl-L-tryptophan, 1218-34-4; *N*-acetyl-L-norvaline, 15891-50-6; hippuric acid, 495-69-2; *trans*-cinnamoyl-DL-alanine, 84064-16-4; *N*-acetyl-L-valine, 96-81-1; 2-chloro-*trans*-cinnamoyl-DL-alanine, 84041-42-9; *N*-acetyl-DL-valine, 3067-19-4; 2-chloro-*trans*-cinnamoyl-L-alanine, 84041-43-0.

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Quenching of Triplet States of Organic Compounds by Chromium(III) Tris(hexafluoroacetylacetonate) in Benzene Solution as a Result of Energy and Electron Transfer

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Contribution from the Department of Chemistry, University of Technology, Loughborough, Leicestershire, England. *Received June 2, 1982*

Abstract: Rate constants for quenching of the triplet states of 13 organic compounds by chromium(III) tris(hexafluoroacetylacetonate), $Cr(hfac)_3$, in benzene solution have been measured using the technique of laser flash photolysis. $Cr(hfac)_3$ is shown to be a very efficient triplet quencher, and even triplets with energies much lower than the lowest excited state of $Cr(hfac)_3$ give relatively high quenching constants, i.e., $\sim 6 \times 10^8$ dm^3 mol^{-1} s^{-1}. For five of the organic triplet donors a limiting quenching constant of 8.2×10^9 dm^3 mol^{-1} s^{-1} was observed. Spin–spin combinations are considered and the results interpreted in terms of quenching involving a combination of energy and electron transfer. It is proposed that quenching by electron transfer in benzene solution involves transfer to $Cr(hfac)_3$ (which is a much better electron acceptor than $Cr(acac)_3$, for which this type of quenching is negligible), followed by rapid reverse transfer ($k_{bt} > 10^8$ s^{-1}) to yield ground-state species. In the exciplex $D^+\cdots Q^-$, formed by electron transfer, $Q^- \equiv [Cr(hfac)_3]^-$ which is likely to be a high-spin Cr(II) complex, and therefore electron transfer via spin combinations which produce doublet states is likely to be prohibited energetically. The values obtained for the transmission coefficients and "intrinsic barriers" for both energy and electron transfer to $Cr(hfac)_3$ from these organic donors are similar to values reported for these parameters for analogous systems where either only energy or only electron transfer occurred. Finally it is suggested that where, as in the case of β-carotene, in this work it is not possible to measure the one-electron oxidation potential directly, the sensitivity of the rate constant dependence on $\Delta G^{\ominus}_{el}$ can be used as a method to obtain a good estimate for E_D^{ox}. Thus E^{ox} for β-carotene is estimated to be 0.35 ± 0.03 V (vs. SCE).

Introduction

In fluid solution transition metal complexes often quench electronically excited states with high efficiency, and the two most prevalent quenching mechanisms have been shown to involve electron[1,2] and energy transfer.[3] Variations in ligand structure as well as in the electronic configuration of the central metal atoms affect the quenching efficiencies by both these mechanisms. Many studies have been carried out to establish the parameters deter-

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