C, 83.10; H, 7.28. Found: C, 83.12; H, 7.13.

Benzaldehyde dioctyl acetal (5h): bp 155 °C (0.015 mmHg); IR (liquid film) 1360 (m), 1115 (s), 1040 (s), 760 (m), 710 (s) cm^{-1}; ^1H NMR δ 0.8-1.8 (30 H, m), 3.5 (4 H, br t, J = 6 Hz), 5.5 (1 H, s), 7.3 (5 H, m); mass spectrum, m/e (relative intensity) 219 ($M^+ - C_8H_{17}O$, trace), 106 (45), 105 (50), 57 (97), 56 (99), 43 (97), 41 (100). Anal. Calcd for $C_{23}H_{40}O_2$: C, 79.25; H, 11.57. Found: C, 79.35; H, 11.70.

2-Methoxymethyl-3-phenyloxirane (4j): bp 130 °C (2.5 mmHg); IR (liquid film) 1460 (s), 1115 (s), 880 (s), 750 (s), 700 (s) cm^{-1}; ^1H NMR δ 3.1-3.9 (6 H, m, including s at 3.23 and 3.43 and d at 3.77, J = 2 Hz, trans), 4.10 (1 H, d, J = 4 Hz, cis), 7.30, 7.33 (5 H, br s); mass spectrum, m/e (relative intensity) 164 (M^+, 16), 132 (46), 104 (56), 103 (100). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.07; H, 7.45.

Benzaldehyde di-2-methoxyethyl acetal (5j): bp 86 °C (0.02 mmHg); IR (liquid film) 1370 (m), 1140 (s), 1105 (s), 1070 (s), 760 (s), 705 (s) cm^{-1}; ^1H NMR δ 3.39 (6 H, s), 3.64 (8 H, m), 5.69 (1 H, s), 7.4 (5 H, m); mass spectrum, m/e (relative intensity) 165 ($M^+ - CH_3OCH_2CH_2$, 33), 105 (10), 59 (100). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.18; H, 8.50.

1-Phenyl-3-penten-1-one (6): bp 115 °C (2.5 mmHg); IR (liquid film) 1690 (s), 1210 (s), 970 (s), 740 (s), 700 (s) cm^{-1}; ^1H NMR δ 1.70 (3 H, br d, J = ca. 4 Hz), 3.7 (2 H, m), 5.65 (2 H, m), 7.3 (3 H, m), 7.85 (2 H, m); mass spectrum, m/e (relative intensity) 160 (M^+, 11), 120 (17), 105 (100), 78 (70).

Reaction of Potassium Benzyl Oxide with $PhCHCl_2$ in the Absence of t-BuOk. A reaction of potassium benzyl oxide (5 mmol) with $PhCHCl_2$ (2 mmol) was performed by a procedure similar to that described above in the absence of t-BuOK at 0 °C for 1 h. VPC analysis showed 78% recovery of $PhCHCl_2$, and 42.4 mg (11%) of diphenyloxirane (**4a**) and 476 mg (88%) of benzyl alcohol were obtained after column chromatography (benzene-ethyl acetate gradient).

2-Chloro-1,2-diphenylethanol (12).[24] To a THF (5 mL) solution of $PhCHCl_2$ (2 mmol) was added slowly 2.2 mol of BuLi (1.55 M hexane solution) at -90 °C under nitrogen atmosphere, and the reaction mixture was stirred for 0.5 h at the same temperature. To this was added a THF (5 mL) solution of lithium benzyl oxide (5 mmol, prepared from benzyl alcohol and BuLi) at -90 °C, and the mixture was slowly warmed up to -10~10 °C within 3.5 h. After the addition of brine followed by extractive workup and column chromatography (cyclohexane-benzene gradient) 129 mg (28%) of **12** (mixture of isomers) was obtained: bp 106 °C (0.015 mmHg); IR (liquid Film) 3420 (br), 1060 (s), 760 (m), 730 (s), 705 (s) cm^{-1}; ^1H NMR δ 2.60, 3.15 (1 H, br), 4.9 (2 H, m), 7.2 (10 H, m); mass spectrum, m/e (relative intensity) 196 (M^+ - HCl, 6), 194 (6), 167 (100), 165 (40), 105 (63). Anal. Calcd for $C_{14}H_{13}OCl$: C, 72.26; H, 5.63. Found: C, 72.54; H, 5.63. 2-Chloro-1,2-diphenylethanol (**12**) (67.6 mg, 0.29 mmol) thus obtained was treated with t-BuOK (0.35 mmol) in THF at 0 °C for 0.5 h to give 53.3 mg (94%) of **4a** (trans:cis = ca. 1).

Isomerization of 2-Benzyl-3-phenyloxirane (4g) to 3-Phenylproplophenone (7). To a THF (8 mL) solution of 120 mg (1.07 mmol) of t-BuOK was added a solution of 150 mg (0.71 mmol) of **4g** (trans:cis = ca. 1) at 0 °C under nitrogen atmosphere, and the mixture was stirred for 0.75 h. After the usual workup followed by column chromatography (cyclohexane-benzene gradient), 137 mg of the mixture of **4g** and **7** was obtained. Yield of **7** based on the consumed **4g** was 90% (determined by ^1H NMR spectroscopy, conversion of **4g** was 89%).

Isomerization of 2-Phenyl-3-(1-propenyl)oxirane (4d) to 1-Phenyl-3-penten-1-one (6). Starting with 150 mg (0.94 mmol) of **4d** (trans:cis = ca. 1) by the similar procedure as described above, 19.3 mg of **6** (40% yield based on the consumed **4d**) was obtained besides the recovery of **4d** (102 mg, conversion 32%) afte florisil column chromatography (cyclohexane-benzene gradient).

Treatment of Benzyl Dichloromethyl Ether with t-BuOLi. Benzyl dichloromethyl ether[25] (9 mmol) that was dissolved in 3 mL of THF was added to a solution of t-BuOLi (9 mmol in 7 mL of THF-hexane) at 0 °C under a nitrogen atmosphere. After being stirred at 70-80 °C for 30 min, the reaction was quenched by adding water. After workup, the product mixture was analyzed by VPC using reference compounds (benzyl chloride, **1a**, and starting ether). Benzyl chloride was the major product (74%) besides small amounts of benzyl alcohol and some high-boiling products in which **1a** was not detected at all.

Acknowledgment. This research was supported by a Grant-in-Aid for Special Project Research (No. 57218013) from the Japan Ministry of Education. We are indebted to Professor S. Oka of Kyoto Unversity for combustion analysis.

Registry No. 1a, 2612-36-4; **1b**, 58622-56-3; **1c**, 84987-59-7; **1d**, 84987-60-0; **1e**, 84987-61-1; **1f**, 84987-62-2; **1g**, 84987-63-3; **1h**, 62836-22-0; **1i**, 84987-64-4; **1j**, 84987-65-5; **2**, 64670-26-4; **3**, 52815-11-9; *cis*-**4a**, 1689-71-0; *trans*-**4a**, 1439-07-2; *cis*-**4b**, 70332-50-2; *trans*-**4b**, 28291-10-3; *cis*-**4c**, 21699-63-8; *trans*-**4c**, 21699-64-9; *cis*-**4d**, 53274-96-7; *trans*-**4d**, 53274-97-8; *cis*-**4e**, 81411-53-2; *trans*-**4e**, 81411-56-5; *cis*-**4f**, 53226-69-0; *trans*-**4f**, 53226-68-9; *cis*-**4g**, 65095-04-7; *trans*-**4g**, 65095-03-6; *cis*-**4h**, 65094-94-2; *trans*-**4h**, 65094-93-1; **4i**, 10152-58-6; *cis*-**4j**, 84987-66-6; *trans*-**4j**, 84987-67-7; **5g**, 84987-68-8; **5h**, 84987-69-9; **5j**, 71412-83-4; **6**, 73481-93-3; **7**, 1083-30-3; **12**, 54060-36-5; $PhCH_2OLi$, 15082-42-5; (*p*-anisyl)CH_2OLi, 57965-13-6; $H_2C{=}CHCH_2OLi$, 52203-12-0; (*E*)-$H_3CCH{=}CHCH_2OLi$, 84987-70-2; (*E*)-$PhCH{=}CHCH_2OLi$, 84987-71-3; (*E*)-$C_{15}H_{31}CH{=}CHCH_2OLi$, 84987-72-4; $H_2C{=}C(CH_3)CH_2OLi$, 84987-73-5; $(CH_3)_2C{=}CHCH_2OLi$, 84987-74-6; (*E*)-$PhCH{=}CHCH(CH_3)OLi$, 84987-75-7; $PhCH_2CH_2OLi$, 15082-43-6; $PhCH_2OK$, 22379-62-0; *p*-$ClC_6H_4CH_2OK$, 73447-13-9; $H_2C{=}CHCH_2OK$, 33374-41-3; *trans*-$CH_3CH{=}CHCH_2OK$, 79695-50-4; $H_2C{=}C(CH_3)CH_3OK$, 84987-76-8; $H_2C{=}CHCH(CH_3)OK$, 79695-48-0; $PhCH_2CH_2OK$, 2245-69-4; *n*-$C_7H_{15}CH_2OK$, 56281-85-7; $(CH_3)_2CHOK$, 6831-82-9; $CH_3OCH_2CH_2OK$, 20246-66-6; dichlorocarbene, 1605-72-7; chlorophenylcarbene, 19807-41-1.

(24) Imura, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 2505.

(25) Gross, H.; Rieche, A.; Hoft, E.; Beyer, E. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5, p 365.

Interdependence of Carbon-Nitrogen and Carbon-Oxygen Bond Lengths in Urea Structures and in Ureido Ring Structures

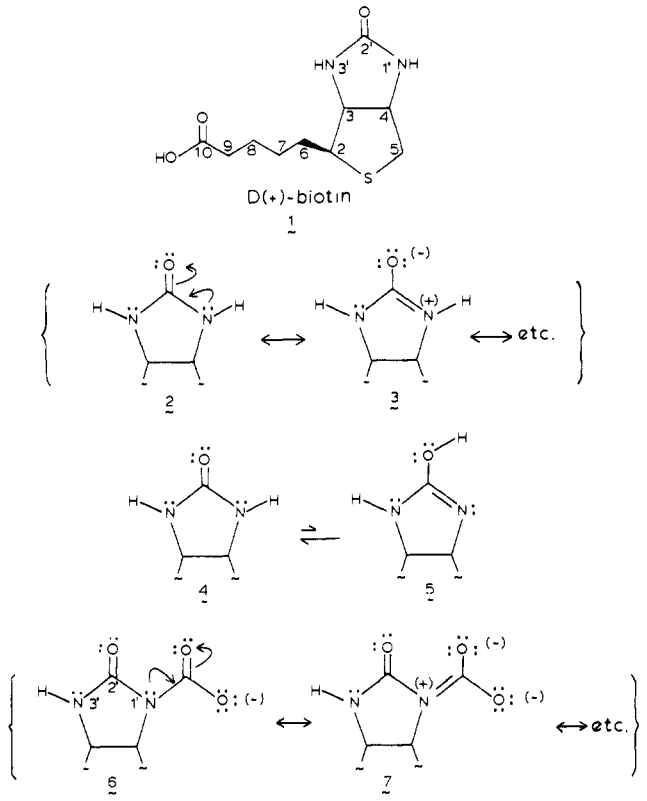
Robert H. Blessing

Contribution from the Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, New York 14203. *Received September 30, 1982*

Abstract: Crystallographic data on the C-N and C-O bond lengths in the N-C(O)-N group in 114 urea and ureido ring structures are analyzed and interpreted in terms of classical valence-bond chemical structures. Substituent effects, the effect of ureido ring closure, and hydrogen-bonding effects are discernible. The structural data have implications for interpretation of the chemical mechanism of the coenzyme biotin.

In connection with studies of the structural biochemistry of biotin (**1**), we have surveyed the crystallographic literature on urea and ureido ring structures. We find that the C-N and C-O bond lengths in these structures clearly illustrate certain basic chemical

0002-7863/83/1505-2776$01.50/0



principles that bear on the mechanism of biotin's biochemical action.

Biotin is coenzyme in a number of metabolic enzyme systems that catalyze various carboxylation, decarboxylation, and transcarboxylation reactions. In these reactions, biotin functions as carbon dioxide shuttle by alternately binding and releasing a labile carboxyl group at N1′. Carboxyl binding and release occur at separate enzymic sites, and translocation between sites occurs via an $N^{1\prime}$-carboxybiotin intermediate. The exact sequence of bond-making and bond-breaking events during biotin enzyme catalysis[1] is not yet fully understood, but the particular features of the chemical and electronic structure of the ureido ring of biotin are important in all mechanistic hypotheses.

In the language of classical valence-bond chemical structures, there are two formal means of electronic coupling between the reactive nitrogen and oxygen atoms of the ureido ring of biotin: First, there is electron delocalization through resonance of canonical structures (**2**, **3**). Second, chemical equilibrium between keto-like (**4**) and enol-like (**5**) tautomers is possible. Both these schemes imply interdependence of the C–N and C–O bond orders and hence of the corresponding bond lengths.

Data and Calculations

We have compiled data from more than 100 crystal structure analyses of urea and ureido ring structures. To the best of our knowledge, our coverage of the literature is comprehensive for urea itself, for the several crystal complexes of urea with simple acids and for biotin and its various analogues. Urea–cation complexes in crystals have been reviewed recently by Lebioda,[2] and we have included in our analysis only structures that Lebioda cited as having estimated standard deviations smaller than 0.01 Å in the urea bond lengths. For molecular crystal complexes with urea and for substituted ureas and urea analogues, we examined only a representative sample of the available data.

The bond lengths are listed in Table I (see also Table II). In the urea crystal structure and in a few of the other structures, the two ureido C–N bonds are equivalent by crystallographic symmetry. In all the other structures the two C–N bonds are not crystallographically equivalent, but we assumed them to be chemically equivalent and averaged the two bond lengths according to

$$\bar{l} = \sum_i (l_i/\sigma_i^2)/\sum_i (1/\sigma_i^2) \quad (1)$$

where σ_i is the estimated standard deviation of the bond length l_i. This weighted mean bond length was assigned as its estimated standard deviation the larger of the two values σ_{internal} and σ_{external}, where

$$\sigma_{\text{internal}}^2(\bar{l}) = 1/\sum_i (1/\sigma_i^2) \quad (2)$$

$$\sigma_{\text{external}}^2(\bar{l}) = (n-1)^{-1}\sum_i [(l_i - \bar{l})^2/\sigma_i^2]/\sum_i (1/\sigma_i^2) \quad (3)$$

with $n = 2$. The question of the validity of assuming equivalence of the two C–N bonds in unsymmetrically substituted ureas and urea analogues is discussed below.

Most of the data in Table I are from room temperature X-ray studies; the several studies that were carried out at low temperatures or with neutrons are so indicated in the table. Small systematic differences between results from these different kinds of experiments can be expected. These effects are discussed in the Appendix, but for the data of Table I the expected differences generally fall within the limits of the random experimental errors. This is especially the case because the estimated standard deviations given in Table I are likely to be underestimates of the experimental errors, by perhaps as much as a factor of two in some cases.[3-5]

The data from Table I are plotted in Figure 1 along with a least-squares line through the data. This line was calculated by using an algorithm[6] that allows for errors in both the x and y coordinates of the data points. The algorithm finds the intercept and slope for the line, $y = a + bx$, by minimizing the residual

$$\sum [w_x(x_{\text{obsd}} - x_{\text{calcd}})^2 + w_y(y_{\text{obsd}} - y_{\text{calcd}})^2] \quad (4)$$

where the weights are

$$w_x = 1/\sigma^2(x_{\text{obsd}}) \text{ and } w_y = 1/\sigma^2(y_{\text{obsd}}) \quad (5)$$

If the weights are unit weights, the algorithm minimizes the sum of squares of the *perpendicular* distances of the observed points from the calculated line. The more usual least-squares straight-line fit assumes that the observed x values have negligible errors compared to the observed y values and minimizes the weighted sum of squares of the *vertical* distances of the points from the line. The minimization of (4) is not a linear least-squares problem, except in various special cases,[6] and the parameters a and b must be refined iteratively. The problem is linear in the case $\sigma(x_{\text{obsd}}) = \sigma(y_{\text{obsd}}) =$ a constant, i.e., the case for which unit weights are appropriate. In our calculations, we used the parameters obtained with unit weights as starting values for the iterative minimization of (4).

To measure the correlation of the data, we calculated the linear correlation coefficient

$$r = \frac{\sum (x_{\text{obsd}} - \bar{x})(y_{\text{obsd}} - \bar{y})}{[\sum (x_{\text{obsd}} - \bar{x})^2 \sum (y_{\text{obsd}} - \bar{y})^2]^{1/2}} \quad (6)$$

where $\bar{x}$ and $\bar{y}$ are the simple, unweighted arithmetic means. The range of r is $-1 \le r \le +1$, the sign of r being the same as the sign of the slope of the line through the data. For perfectly correlated data $|r| = 1$, but smaller values of $|r|$ can still be highly significant if the number of data is large. To interpret r, we also calculated

(1) Moss, J.; Lane, M. D. In "Advances in Enzymology"; Meister, A., Ed.; Interscience Publishers: New York, 1971; Vol. 35, pp 321–442.
(2) Lebioda, L. *Acta Crystallogr., Sect. B* **1980**, *B36*, 271–275.
(3) Hughes, E. W. In "Structural Chemistry and Molecular Biology"; Rich, A.; Davidson, N., Eds.; W. H. Freeman and Co.: San Francisco, 1968; pp 626–628.
(4) Abrahams, S. C. *Acta Crystallogr., Sect. B* **1974**, *B30*, 261–268.
(5) Shoemaker, D. P. In "Critical Evaluation of Chemical and Physical Structural Information"; Lide, D. R., Jr., Paul, M. A., Eds.; U.S. National Academy of Sciences: Washington, D.C., 1974; pp 177–180.
(6) York, D. *Can. J. Phys.* **1966**, *44*, 1079–1086.

Table I. Averaged C-N vs. C-O Bond Lengths (Angstroms) in Urea Structures and Ureido Ring Structures[a]

<C-N>	C-O	Crystal Structure	Reference
Urea			
1.326(6)	1.270(7)	urea	75, 10, 11
1.351(7)	1.243(6)	urea (n)	84
1.336(7)	1.264(6)	urea	67
1.341(3)	1.262(3)	urea (133 K)	67
1.351(17)	1.281(17)	urea (e-)	52
1.332(2)	1.253(3)	urea (n)	63
1.338(2)	1.250(3)	urea (n)	63
1.350(2)	1.257(3)	urea-d4 (n)	63
1.336(4)	1.251(5)	urea	11, 63
1.338(4)	1.262(3)	urea (123 K)	57
1.333(1)	1.246(2)	urea (293 K) (n)	32
1.339(1)	1.258(2)	urea (123 K) (n)	32
1.344(2)	1.258(4)	urea (60 K) (n)	32
1.3377(15)	1.2566(18)	Averaged Urea	
Urea-Acid Complexes			
1.329(3)	1.261(3)	(urea)2.H2C2O4	34, 35
1.332(1)	1.261(2)	urea.H2C2O4	36
1.3317(9)	1.2610(16)	Averaged Urea-Oxalic Acid	
1.332(8)	1.290(10)	urea.H3PO4	72
1.38(3)	1.27(2)	urea.H3PO4	82
1.3235(14)	1.281(3)	urea.H3PO4 (n)	44
1.3215(25)	1.278(3)	urea.H3PO4	56
1.316(4)	1.278(5)	urea.H3PO4 (n)	60
1.321(3)	1.2786(25)	Averaged Urea-Phosphoric Acid	
1.3135(15)	1.298(2)	urea.HNO3 (n)	83
1.302(4)	1.302(3)	urea.HNO3	38
1.3075(21)	1.307(3)	urea.HNO3	38
1.304(6)	1.306(3)	urea.HNO3	80
1.3106(22)	1.298(5)	Averaged Urea-Nitric Acid	
Urea-Molecular Complexes			
1.3399(3)	1.2609(5)	urea.H2O2 (81 K) (n)	26
1.325(21)	1.306(16)	urea.(1,4-dichlorobutane)	61
1.321(16)	1.269(23)	urea.(1,4-dichlorobutane)	61
1.3335(21)	1.253(2)	urea.quinol	53
1.326(8)	1.253(6)	urea.estradiol	24
1.330(8)	1.246(5)	urea.(alpha-D-glucose)	68
1.338(6)	1.238(3)	urea.barbital	27
1.3425(7)	1.250(1)	urea.Parabanic acid (116 K) (n)	79
1.330(4)	1.245(5)	urea.tetracycline	69
1.324(7)	1.260(2)	urea.Cu(formate)2.H2O	43
1.324(6)	1.265(6)	4urea.Mg(urea)6 Br2	49
1.342(6)	1.249(6)	4urea.Mg(urea)6 Br2	49
1.3400(6)	1.2529(17)	Averaged Urea in Molecular Complexes	
Urea-Salt Crystalline Adducts (Urea-Cation Complexes)			
1.358(12)	1.246(6)	Mg(urea)6 Br2.4urea	49
1.335(15)	1.243(6)	Mg(urea)6 Br2.4urea	49
1.342(8)	1.256(6)	Mg(urea)6 Br2.4urea	49
1.332(9)	1.251(2)	Mg(H2O)2 (urea)4 Br2	48
1.330(10)	1.252(2)	Mg(H2O)2 (urea)4 Br2	48
1.335(2)	1.255(2)	Ca(urea)4 (NO3)2	46
1.333(3)	1.255(2)	Ca(urea)4 (NO3)2	46
1.349(4)	1.254(5)	Ca(urea)4 SO4	23
1.347(15)	1.260(5)	Ca(urea)4 SO4	23
1.327(20)	1.245(5)	Ca(urea)4 SO4	23
1.346(14)	1.254(5)	Ca(urea)4 SO4	23
1.332(4)	1.256(4)	Ca(urea)6 Br2	46
1.335(4)	1.242(4)	Ca(urea)6 Br2	46
1.322(7)	1.255(4)	Ca(urea)6 Br2	46
1.327(5)	1.263(5)	Zn(urea)6 (NO3)2	28
1.343(6)	1.254(5)	Zn(urea)6 (NO3)2	28
1.335(4)	1.258(4)	Zn(urea)6 (NO3)2	28
1.3349(19)	1.2532(10)	Averaged Urea in Cation Complexes	
Symmetrically Substituted Ureas			
1.341(5)	1.252(7)	N,N'-dicyclohexylurea	13
1.348(8)	1.234(4)	N,N'-diphenylurea	19
1.370(3)	1.220(7)	N,N'-bis(p,p,p-trinitro-Et)urea	51
1.366(4)	1.211(4)	N,N'-di-Me-N,N'-di(PNPH)urea	50
1.390(6)	1.175(6)	N,N'-di-Me-N,N'-di(2,4-DNPH)urea	50
1.364(4)	1.227(4)	N,N'-bis(3,4-di-Cl-Ph)urea	71
1.369(3)	1.222(4)	N,N'-bis(3,4-di-Cl-Ph)urea	71
1.372(7)	1.243(8)	N,N'-bis(a-Ts-Bz)urea.acetone	73
1.366(11)	1.216(12)	N,N'-bis(Ts-Me)urea	77

C-N	C-O	Crystal Structure	Reference
Unsymmetrically Substituted Ureas			
1.338(2)	1.248(1)	N-methylurea	40
1.328(8)	1.269(2)	(N-methylurea)2.H2C2O4 (Pnma)	37
1.334(8)	1.260(2)	(N-methylurea)2.H2C2O4 (Pnma)	37
1.326(6)	1.266(3)	(N-methylurea)2.H2C2O4 (P21/c)	37
1.295(14)	1.280(20)	N-methylurea.HNO3	8
1.338(4)	1.241(5)	L-citrulline.HCl	3
1.348(4)	1.243(5)	L-homocitrulline.HCl	3
1.338(10)	1.255(1)	N-hydroxyurea (n)	74
1.333(3)	1.254(4)	N-hydroxyurea	2
1.340(6)	1.263(3)	N-hydroxyurea (133 K)	2
1.335(3)	1.253(4)	N-hydroxyurea	4
1.33(4)	1.265(10)	N-hydroxyurea	45
1.350(24)	1.245(9)	N-phenylurea	42
1.344(16)	1.242(2)	acetone semicarbazone	58
1.350(20)	1.239(3)	benzaldehyde semicarbazone	58
1.361(19)	1.230(2)	carbamazepine	64
1.37(3)	1.218(3)	N-p-Cl-Ph-N'-(2,6-di-F-Bzoyl)urea	18
1.36(4)	1.239(4)	N-i-Pr-N'-Ar-sulfonylurea	25
1.364(6)	1.225(2)	N-bicyclo-R-N',N'-dimethylurea	33
1.364(8)	1.234(3)	N-bicyclo-R-N',N'-dimethylurea	33
1.324(12)	1.310(9)	O-methylpseudourea.HCl	81
Urea Analogs			
1.354(15)	1.249(4)	biurea	7
1.365(14)	1.230(5)	triuret	9
1.352(16)	1.248(4)	D,L-allantoin	55
1.360(7)	1.241(8)	potassium allantoinate	65
1.390(1)	1.199(1)	parabanic acid	16
1.379(3)	1.213(1)	parabanic acid.urea (116 K) (n)	79
1.372(1)	1.220(2)	cyanuric acid (90 K)	76
1.370(1)	1.217(1)	cyanuric acid (125 K) (n)	15
1.3719(19)	1.2096(14)	barbiturates (average of 14)	17
1.371(4)	1.232(1)	3-hydroxyxanthine dihydrate	74
1.374(5)	1.218(4)	pyrimidinetrione derivative	1
Ureido Ring Structures (Biotin, Biotin Vitamers, and Analogs)			
1.343(7)	1.250(6)	biotin	21
1.338(12)	1.247(6)	biotin	21
1.341(5)	1.248(4)	Averaged Biotin	
1.346(3)	1.244(4)	dethiobiotin	12
1.348(3)	1.239(4)	carbobiotin	22
1.346(3)	1.243(4)	azabiotin hydrochloride	30
1.329(4)	1.269(7)	oxybiotin	22
1.351(5)	1.236(6)	biotin methyl ester	22
1.352(4)	1.233(4)	biotin sulfoxide	22
1.356(7)	1.223(8)	biotin sulfone	22
1.357(7)	1.235(10)	selenobiotin	22
1.3460(18)	1.2415(30)	Averaged Biotin and Biotin Vitamers	
1.339(3)	1.244(2)	biotine sans chaine	20
1.348(2)	1.237(2)	oxybiotine sans chaine	20
1.348(2)	1.233(2)	oxybiotine sans chaine	20
1.342(2)	1.246(3)	azabiotin without chain	20
1.350(1)	1.245(2)	glycoluril (Cmcm)	5
1.348(4)	1.243(2)	glycoluril (Pnma)	5
1.338(2)	1.237(3)	3a,6a-dimethylglycoluril	39
1.3465(13)	1.2408(14)	Averaged Biotin and Biotin Analogs	
N1'-Carboxybiotins			
1.396(28)	1.163(40)	carboxybiotin bis(p-Br-anilide)	6
1.370(24)	1.207(9)	carboxybiotin bis(Me ester)	70
1.380(36)	1.206(9)	carboxybiotin bis(Me ester)	70
1.375(14)	1.205(6)	Averaged N1'-Carboxybiotins	

[a] See Table II for reference list.

the probability p that a random sample of n uncorrelated data points would give a correlation coefficient with magnitude as large as or larger than $|r|$

$$p(|r|,n) = \frac{1}{\pi^{1/2}} \frac{\Gamma[(\nu+1)/2]}{\Gamma(\nu/2)} \int_{|r|}^{1} (1-x^2)^{(\nu-2)/2}\, dx \qquad (7)$$

where $\nu = n - 2$ and Γ is the gamma function.[7]

Averaged bond lengths for various groups of chemically equivalent molecules are included in Table I. These groups means were calculated by using (1), and their estimated standard deviations were taken to be the larger of the values from (2) and (3). The group means were not included in the least-squares fit shown in Figure 1, but they were fitted separately as shown in Figure 2.

(7) Bevington, P. R. "Data Reduction and Error Analysis for the Physical Sciences"; McGraw-Hill Book Co.: New York, 1969; pp 122 ff.

Results and Discussion

Overall Trends. As shown in Figures 1 and 2, the C–N and C–O bond lengths in urea and ureido ring structures—and in a chemical variety of analogous structures as well—vary approximately inversely through a range of about 1.30–1.40 Å for l(C–N) and 1.20–1.30 Å for l(C–O). These bond lengths variations of ~0.1 Å indicate a considerable variation of electronic structure.

Table II. References

(1) Arreda, M.C.; Cano, F.H.; Foces-Foces, C.; Garcia-Blanco, S. Acta Crystallogr. Sect. B 1981, B37, 1935-1938.

(2) Arnason, N.; Richards, J.P.G.; Uraz, A.A. Acta Crystallogr. Sect. B 1976, B32, 1042-1047.

(3) Ashida, T.; Funakoshi, K.; Tsukihara, T.; Ueki, T.; Kakudo, M. Acta Crystallogr. Sect. B 1972, B28, 1367-1373.

(4) Berman, H.; Kim, S.H. Acta Crystallogr. 1967, B23, 180-181.

(5) Blessing, R.H.; DeTitta, G.T. American Crystallographic Association Meeting, Boston, Mass., Aug. 1979, Abstract No. S10. Acta Crystallogr. Sect. B 1982 in press.

(6) Bonnemere, C.; Hamilton, J.A.; Steinrauf, L.K.; Knappe, J. Biochem. 1965, 4, 240-245.

(7) Brown, D.S.; Russell, P.R. Acta Crystallogr. Sect. B 1976, B32, 1056-1058.

(8) Bryden, J.H. Acta Crystallogr. 1957, 10, 714.

(9) Carlstrom, D.; Rinsertz, H. Acta Crystallogr. 1965, 18, 307-313.

(10) Caron, A.; Donohue, J. Acta Crystallogr. 1964, 17, 544-546.

(11) Caron, A.; Donohue, J. Acta Crystallogr. Sect. B 1969, B25, 404.

(12) Chen, C.-S.; Parthasarathy, R.; DeTitta, G.T. J. Am. Chem. Soc. 1976, 98, 4983-4990.

(13) Coiro, V.M.; Giacomello, P.; Giglio, E. Acta Crystallogr. Sect. B 1971, B27, 2112-2119.

(14) Coleman, P.M.; Medlin, E.H. Acta Crystallogr. Sect. B 1970, B26, 1547-1553.

(15) Coppens, P.; Vos, A. Acta Crystallogr. Sect. B 1971, B26, 146-158.

(16) Craven, B.M.; Mc Mullan, R.K. Acta Crystallogr. Sect. B 1979, B35, 934-935.

(17) Craven, B.M.; Cusatis, C.; Gartland, G.L.; Vizzini, E.A. J. Mol. Struct. 1973, 16, 331-342.

(18) Cruse, W.B.T. Acta Crystallogr. Sect. B 1978, B34, 2904-2906.

(19) Dannecker, W.; Kopf, J.; Rust, H. Cryst. Struct. Comm. 1979, 8, 429-432.

(20) DeTitta, G.T.; Blessing, R.H. American Crystallographic Association Meeting, Boston, Mass., Aug. 1979, Abstract No. S5.

(21) DeTitta, G.T.; Edmonds, J.W.; Stallings, W.; Donohue, J. J. Am. Chem. Soc. 1976, 98, 1920-1926.

(22) DeTitta, G.T.; Parthasarathy, R.; Blessing, R.H.; Stallings, W.C. Proc. Natl. Acad. Sci. USA 1980, 77, 333-337.

(23) DeVilliers, J.P.R.; Bowens, J.C.A. J. Cryst. Mol. Struct. 1975, 5, 215-226.

(24) Duax, W.L. Acta Crystallogr. Sect. B 1972, B28, 1864-1871.

(25) Dupont, L.; Dideberg, O.; Vermeire, M. Acta Crystallogr. Sect. B 1979, B35, 1501-1504.

(26) Fritchie, Jr., C.J.; Mc Mullan, R.K. Acta Crystallogr. Sect. B 1981, B37, 1086-1091.

(27) Gartland, G.L.; Craven, B.M. Acta Crystallogr. Sect. B 1974, B30, 980-985.

(28) Giesen, W. van de; Stam, C.H. Cryst. Struct. Comm. 1972, 1, 257-260.

(29) Gilbert, R.E.; Lonsdale, K. Acta Crystallogr. 1956, 9, 697-709; 709-721.

(30) Glick, M.D.; Wormser, H.C.; Abramson, H.N. Acta Crystallogr. Sect. B 1977, B33, 1095-1101.

(31) Grenville-Wells, H.J. Acta Crystallogr. 1956, 9, 709-721.

(32) Guth, H.; Heeser, G.; Klein, S.; Treutmann, W.; Scheringer, C. Z. Kristallogr. 1980, 153, 237-254.

(33) Haltinger, R.C.; Burns, J.M.; Crockett, G.C.; Koch, T.A. J. Am. Chem. Soc. 1978, 100, 5110-5116.

(34) Harkema, S.; Bats, J.W.; Weyenberg, A.M.; Feil, D. Acta Crystallogr. Sect. B 1972, B28, 1646-1648.

(35) Harkema, S.; Bats, J.W.; Weyenberg, A.M.; Feil, D. Acta Crystallogr. Sect. B 1973, B29, 143.

(36) Harkema, S.; Brake, J.H.M. ter. Acta Crystallogr. Sect. B 1979, B35, 1011-1013.

(37) Harkema, S.; Brake, J.H.M. ter; Meutstege, H.J.G. Acta Crystallogr. Sect. B 1975, B35, 2087-2093.

(38) Harkema, S.; Feil, D. Acta Crystallogr. Sect. B 1969, B25, 589-591.

(39) Himes, V.L.; Hubbard, C.R.; Mighell, A.D.; Fatiadi, A.J. Acta Crystallogr. Sect. B 1978, B34, 3102-3104.

(40) Huiszoon, C.; Tiemessen, G.W.M. Acta Crystallogr. Sect. B 1976, B32, 1604-1606.

(41) Ishii, M.; Scheringer, C. Acta Crystallogr. Sect. A 1979, A35, 613-616.

(42) Kashino, S.; Haisa, M. Acta Crystallogr. Sect. B 1977, B33, 855-860.

(43) Kiriwama, H.; Kitahama, K. Acta Crystallogr. Sect. B 1976, B32, 330-333.

(44) Kostansek, E.C.; Busing, W.R. Acta Crystallogr. Sect. B 1972, B28, 2454-2459.

(45) Larsen, I.K.; Jerslev, B. Acta Chem. Scand. 1966, 20, 983-991.

(46) Lebioda, L. Acta Crystallogr. Sect. B 1980, B36, 271-275.

(47) Lebioda, L.; Hodorowicz, S.; Lewinski, K. Phys. Status Solidi A 1978, 49, k27-k30.

(48) Lebioda, L.; Lewinski, K. Acta Crystallogr. Sect. B 1980, B36, 693-695.

(49) Lebioda, L.; Stadnicka, K.; Sliwinski, J. Acta Crystallogr. Sect. B 1979, B35, 157-158.

(50) Lepore, U.; Castronuovo-Lepore, G.; Ganis, P.; Goodman, M. Cryst. Struct. Comm. 1975, 4, 351-354.

(51) Lind, M.D. Acta Crystallogr. Sect. B 1970, B26, 590-596.

(52) Lobachev, A.N.; Vainshtein, B.K. Sov. Phys. Crystallogr. 1961, 6, 313-317; Kristallografiya 1961, 6, 395-401.

(53) Mahmoud, M.M.; Wallwork, S.C. Acta Crystallogr. Sect. B 1975, B31, 338-342.

(54) Mc Kenzie, D.R.; Pryor, A.W. J. Phys. C 1971, 4, 2304-2312.

(55) Mootz, D. Acta Crystallogr. 1965, 19, 726-734.

(56) Mootz, D.; Albrand, K.-R. Acta Crystallogr. Sect. B 1972, B28, 2459-2463.

(57) Mullen, D.; Heilner, E. Acta Crystallogr. Sect. B 1978, B34, 1624-1627.

(58) Naik, D.V.; Palenik, G.J. Acta Crystallogr. Sect. B 1974, B30, 2396-2401.

(59) Niven, M.L.; Nassimbeni, L.R.; Gaffner, G. Cryst. Struct. Comm. 1980, 9, 1133-1140.

(60) Nozik, Yu.Z.; Fykin, I.E.; Bukin, V.I.; Muradyan, L.A. Sov. Phys. Crystallog. 1976, 21, 414-417; Kristallografiya 1976, 21, 730-735.

(61) Otto, J. Acta Crystallogr. Sect. B 1972, B28, 543-551.

(62) Palenik, G.J.; Mathew, M. J. Am. Chem. Soc. 1978, 100, 4464-4469.

(63) Pryor, A.W.; Sanger, P.L. Acta Crystallogr. Sect. A 1970, A26, 543-558.

(64) Rebou, J.F.; Cristau, B.; Soyfer, J.C.; Astier, J.P. Acta Crystallogr. Sect. B 1981, B37, 1844-1848.

(65) Rinsertz, H. Acta Crystallogr. Sect. B 1969, B25, 1686-1692.

(66) Scheringer, C. Acta Crystallogr. Sect. A 1980, A36, 814-818.

(67) Sklar, N.; Senko, M.E.; Post, B. Acta Crystallogr. 1961, 14, 716-720.

(68) Snyder, R.L.; Rosenstein, R.D. Acta Crystallogr. Sect. B 1971, B27, 1969-1975.

(69) Stallings, W.C. Arch. Biochem. Biophys. 1977, 183, 189-199.

(70) Stallings, W.C.; Monti, C.T.; Lane, M.D.; DeTitta, G.T. Proc. Natl. Acad. Sci. USA 1980, 77, 1260-1264.

(71) Stankovic, S.; Andreetti, G.D. Acta Crystallogr. Sect. B 1978, B34, 3787-3790.

(72) Sundera-Rao, R.V.G.; Turley, J.W.; Peiminsky, R. Acta Crystallogr. 1957, 10, 435-436.

(73) Tel, R.M.; Ensberts, J.B.F.N. J. Chem. Soc., Perkin Trans. 2, 1976, 1976, 501.

(74) Thiessen, W.E.; Levy, H.A.; Flais, B.D. Acta Crystallogr. Sect. B 1978, B34, 2495-2502.

(75) Vaughn, P.; Donohue, J. Acta Crystallogr. 1952, 5, 530-535.

(76) Verschoor, G.C.; Keulen, E. Acta Crystallogr. Sect. B 1971, B27, 134-145.

(77) Visser, R.J.J.; Vos, A.; Tel, R.M.; Ensberts, J.B.F.N. Rec. Trav. Chim. Pays-Bas 1978, 97, 181-184.

(78) Wang, A.C.; Craven, B.M. Acta Crystallogr. Sect. B 1979, B35, 510-513.

(79) Weber, H.P.; Ruble, J.R.; Craven, B.M.; Mc Mullan, R.K. Acta Crystallogr. Sect. B 1980, B36, 1121-1126.

(80) White, J.C.B.; Mason, S.A. Unpublished results 1969. As cited in ref. 81.

(81) White, J.C.B.; Mason, S.A. Acta Crystallogr. Sect. B 1970, B26, 2068-2072.

(82) Wolfram, W.; Arutian, E.G.; Antishkina, A.S.; Porai-Koshits, M.A. Bull. Acad. Polonaise Sci., Ser. Sci. Chim. 1967, 15, 83-85.

(83) Worsham, Jr., J.E.; Busing, W.R. Acta Crystallogr. Sect. B 1969, B25, 572-578.

(84) Worsham, Jr., J.E.; Levy, H.A.; Peterson, S.W. Acta Crystallogr. 1957, 10, 319-323.

For molecules represented by data in the upper left of Figures 1 and 2, canonical structures like **3** are important; data in the lower right of the figure correspond to structures like **2**. For comparison, standard estimates[8] of the lengths of single and double bonds, respectively, are 1.47 and 1.25 Å for *l*(C–N) and 1.43 and 1.21 Å for *l*(C–O).

The C–N and C–O bond lengths in peptides tend to follow a trend parallel to that shown by the urea and ureido ring data. This

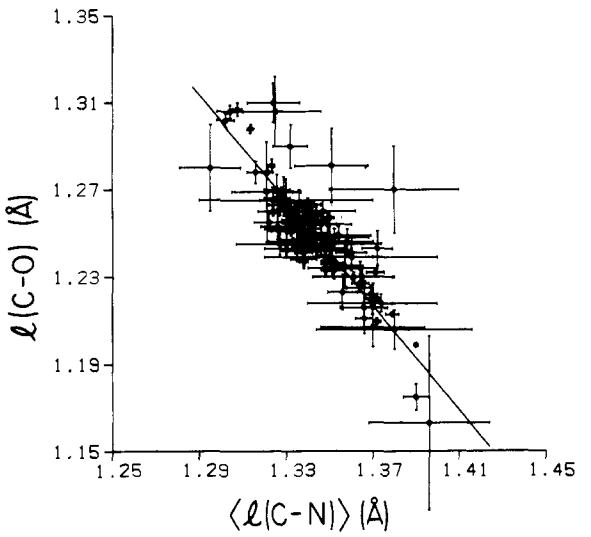


Figure 1. Plot of $y = l(\text{C–O})$ vs. $x = \langle l(\text{C–N})\rangle$ for urea and ureido ring structures from Table I. The correlation statistics for the $n = 114$ data points are $r = -0.83$ and $p(n, |r|) < 0.001$. The equation of the least-squares line is $y = 2.869 - 1.206x$.

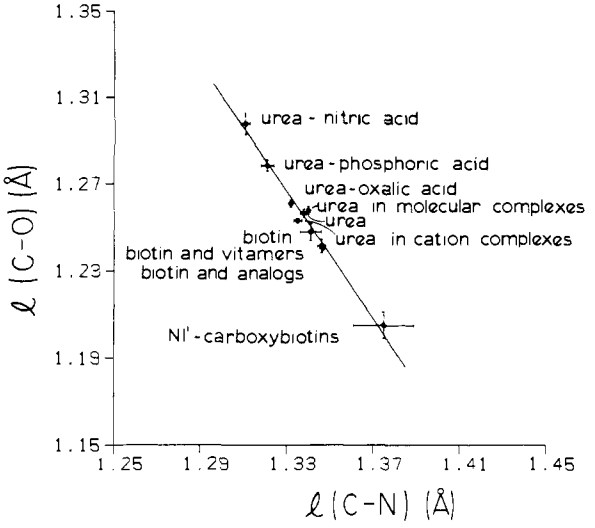


Figure 2. Plot of $y = \langle l(\text{C–O})\rangle$ vs. $x = \langle l(\text{C–N})\rangle$ for bond lengths averaged over groups of chemically equivalent molecules from Table I. The equation of the line is $y = 3.210 - 1.462x$.

is illustrated in Figure 3, where the data compiled by Benedetti[9] for 78 peptide units in 34 crystal structues are plotted. The peptide data vary over a smaller range and are more scattered than the urea and ureido ring data. Still, the linear correlation coefficient for the peptide data is –0.28, and the probability of no correlation for the 78 data is only about 1%.

The trend lines in Figure 3 show that for a given C–N bond length, a carbamide C–O bond in a urea or ureido structure tends to be longer than a corresponding amide C–O bond in a peptide. This is so because for amides there is only one canonical structure analogous to **3**, whereas for carbamides there are two such structures, which are equivalent. Thus, a given C–N shortening causes a greater C–O lengthening in a carbamide than in an amide.

Substituent Effects. As mentioned above, the two ureido C–N bonds are not crystallographically equivalent in most of the structures listed in Table I. In the unsymmetrically substituted structures, the two bonds are not chemically equivalent either, and in these cases averaging the pairs of C–N bond lengths is open to question.

Data pertinent to this question are given in Table III, which

(8) Pauling, L. "The Nature of the Chemical Bond"; 3rd ed.,; Cornell University Press: Ithaca, New York, 1960; pp 93, 224, and 229.

(9) Benedetti, E. In "Peptides, Proceedings of the Fifth American Peptide Symposium"; Goodman, M., Meienhofer, J., Eds.; John Wiley and Sons: New York, 1977; pp 257–273.

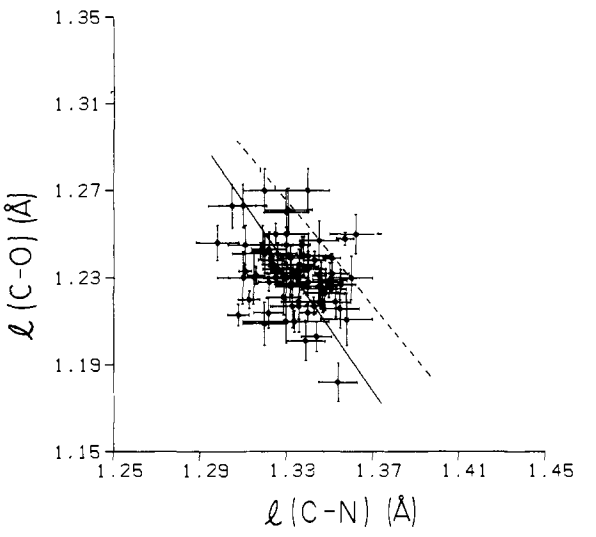


Figure 3. Plot of $y = l(\text{C–O})$ vs. $x = l(\text{C–N})$ for peptide units. Data were compiled by Benedetti.[9] The correlation statistics for the $n = 78$ data points are $r = -0.28$ and $p(n, |r|) = 0.006$. The equation of the solid line is $y = 3.167 - 1.452x$. The dashed line is the line from Figure 1 for the urea and ureido ring structures.

lists pairs of C–N bond lengths and the differences between the individual lengths for the monosubstituted structures from Table I. Although some of the bond length differences are small compared to their estimated standard deviations, the differences are chemically systematic. Thus, (see Table III) *N*-alkyl substitution shortens the ureido C–N bond to the substituted nitrogen, because the electron releasing inductive effect of the alkyl substituent makes the nitrogen lone pair electron density more available for π-bonding, as in **3**. Correspondingly, the electron withdrawing inductive effect of an *N*-hydroxy substituent lengthens the substituted ureido C–N bond. Substituents with a π system conjugated to the ureido π system appear to lengthen the substituted ureido C–N bond by resonance effects. Thus, in the $N^{1\prime}$-carboxybiotin structure (Table III), for example, the resonance of structures like **2** and **3** is largely confined to involvement of the unsubstituted N3′, because the N1′ lone pair density can be delocalized into the carboxyl π system (**6**, **7**).

With their C–N bond lengths averaged, the unsymmetrically substituted structures follow the same trend line (Figure 1) as the unsubstituted and symmetrically substituted structures. This indicates that chemical alteration at one of the ureido nitrogen atoms is compensated by electronic adjustments at the oxygen atom and the other nitrogen atom such that the valence of the central carbon atom remains constant at four.

Effect of Ureido Ring Closure. On the basis of *N*-alkyl substituent effects, it might be expected that in the ureido ring of biotin the C–N bonds would be shorter, and hence the C–O bond longer, than the corresponding bonds in urea. Data in Table I and Figure 2 for biotin and urea show that the opposite is true. This can be rationalized as an effect of ring closure, which also closes the ureido N–C–N bond angle from an average value of 116.8 (2)° in urea to an average 109.0 (2)° in biotin and its analogues. If the central ureido carbon atom is sp^2 hybridized (ideal valence angles 120°), the decrease in the N–C–N bond angles would bend and hence weaken the C–N bonds because of decreased σ-orbital overlap, as indicated in Figure 4. The weakening and lengthening of the C–N bonds are compensated by a shortening and strengthening of the C–O bond.

Effect of Hydrogen Bonding. An important chemical trend is illustrated in Figure 2 by the data points for urea, urea–oxalic acid, urea–phosphoric acid, and urea–nitric acid (uronium nitrate). These points correspond, respectively, to an increasing degree of protonation of the urea oxygen—from a relatively weak hydrogen-bonded association in the urea crystal structure to full protonation in the uronium nitrate crystals (see Figure 5). With this increasing degree of protonation, there is progressive lengthening of the C–O bond and commensurate shortening of

Table III. C-N and C-O Bond Lengths (Angstroms) in Unsymmetrically N-Substituted Ureas

	C-N		difference		ref
	subst	unsubst	(s − u)	C-O	(Table II)
N-alkyl substitution					
N-methylurea	1.336 (2)	1.340 (2)	−0.004 (3)	1.248 (1)	40
(*N*-methylurea)$_2$·$H_2C_2O_4$	1.320 (3)	1.336 (3)	−0.016 (4)	1.269 (2)	37
	1.325 (3)	1.342 (3)	−0.017 (4)	1.260 (2)	37
	1.320 (3)	1.331 (3)	−0.011 (4)	1.266 (3)	37
N-methylurea·HNO_3	1.30 (2)	1.29 (2)	0.01 (3)	1.28 (2)	8
L-citrulline·HCl	1.334 (5)	1.342 (5)	−0.008 (7)	1.241 (5)	3
L-homocitrulline·HCl	1.345 (5)	1.350 (5)	−0.005 (7)	1.243 (5)	3
average			−0.010 (2)		
N-hydroxyurea					
N-hydroxyurea	1.347 (1)	1.328 (1)	0.0190 (14)	1.255 (1)	74
	1.336 (3)	1.330 (4)	0.006 (5)	1.254 (4)	2
	1.347 (3)	1.334 (4)	0.013 (5)	1.263 (3)	2
	1.334 (4)	1.336 (4)	−0.002 (6)	1.253 (4)	4
	1.408 (10)	1.325 (10)	0.083 (14)	1.265 (10)	45
averages	1.346 (3)	1.329 (1)	0.017 (4)	1.2556 (13)	
N-aryl or conjugated, unsaturated substitution					
N-phenylurea	1.375 (10)	1.340 (10)	0.035 (14)	1.245 (9)	42
acetone semicarbazone	1.361 (3)	1.328 (3)	0.033 (4)	1.242 (2)	58
benzaldehyde semicarbazone	1.370 (3)	1.331 (3)	0.039 (4)	1.239 (3)	58
average			0.036 (3)		
$N^{1'}$-carboxybiotins					
bis(*p*-bromoanilide)	1.406 (40)	1.385 (40)	0.021 (56)	1.163 (40)	6
bis(methyl ester)	1.393 (9)	1.346 (9)	0.047 (13)	1.207 (9)	70
	1.416 (9)	1.344 (9)	0.072 (13)	1.206 (9)	70
averages	1.404 (8)	1.346 (6)	0.058 (10)	1.205 (6)	

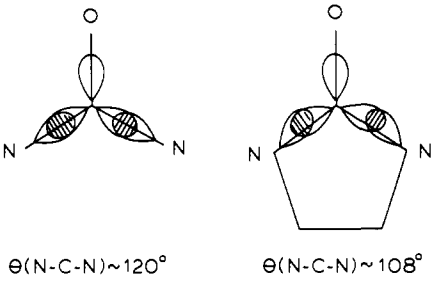
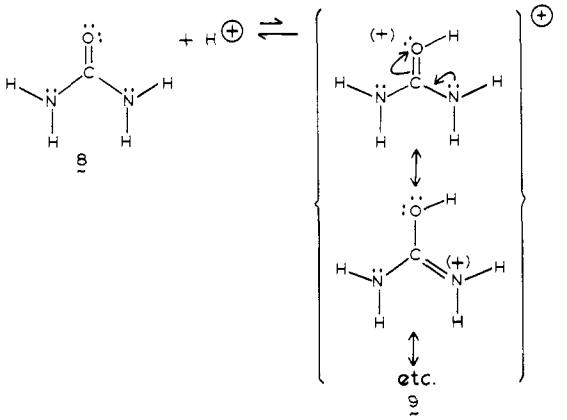


Figure 4. Schematic illustration of bent bonds and decreased σ-orbital overlap in ureido ring structures as compared with urea structures.

the C-N bond (Figure 2), in accord with the scheme of **8** and **9**. Thus, hydrogen bonding or protonation of the urea oxygen



draws the nitrogen lone pair electron density into the π system and strengthens the acidity of the carbamide hydrogens. Ionization of one of these hydrogens would in turn yield an enol-like tautomer like **5** with the imino nitrogen a potent nucleophile.

We have earlier suggested[10] that hydrogen-bond making and hydrogen-bond breaking might be involved in the biochemical energetics of the $N^{1'}$-carboxybiotin translocation in biotin enzymes. We now see that breaking and making hydrogen bonds to the ureido oxygen alters the electronic structure and chemical reactivity around the ureido nitrogens and thus might assist the actual binding and release of the labile $N^{1'}$-carboxyl group. Stallings[11] has described a specific example of an hypothesis for carboxyl binding by biotin based on complementary hydrogen bonding between the uredio group and bicarbonate ion. We

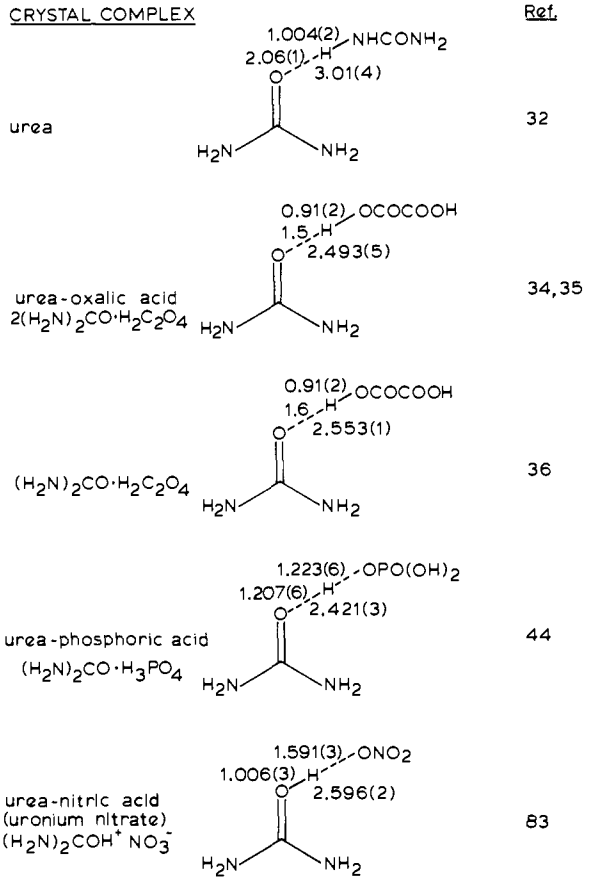


Figure 5. Hydrogen-bond distances (Å) in crystalline complexes of urea with simple acids (see also Table I).

(10) DeTitta, G. T.; Parthasarathy, R.; Blessing, R. H.; Stallings, W. C. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 333–337.

(11) Stallings, W. C. *Arch. Biochem. Biophys.* **1977**, *183*, 189–199.

Table IV. Temperature Dependence of the Lattice Parameters of Urea Crystals[e]

T (K)	a (Å)	c (Å)	wavelength (Å)	footnote	ref (Table II)
60	5.572 (8)	4.686 (8)	n, 1.0327		32
90	5.577 (9)	4.691 (3)	Cu Kα, 1.5418	*a*	29
113	5.578 (2)	4.680 (2)	Cu Kα	*b*	67
123	5.576 (3)	4.686 (3)	Mo Kα, 0.7107		57
123	5.578 (5)	4.695 (5)	n, 1.0202		32
133	5.582 (2)	4.686 (2)	Cu Kα		67
213	5.612 (2)	4.696 (2)	Cu Kα		67
293	5.660 (7)	4.7075 (25)	Cu Kα, 1.5418	*a*	29
293	5.645 (3)	4.704 (3)	n, 0.9213		32
295	5.662 (3)	4.716 (3)	n	*c*	63
295	5.66 (1)	4.71 (1)	e−	*c*	52
295	5.661	4.712	Cu Kα, 1.542	*c, d*	75
301	5.662 (2)	4.716 (2)	Cu Kα		67
370	5.691 (13)	4.716 (4)	Cu Kα, 1.5418	*a*	29

[a] The lattice parameters were calculated by us by least-squares fit to d spacings reported by Gilbert and Lonsdale.[29] [b] If no numerical wavelength value is listed, none was reported by the original authors. [c] We assumed $T = 295$ K for "room temperature". [d] Vaughn and Donohue[75] did not report esd's, so we assigned esd's of 0.003 Å for the least-squares fitting of the curves shown in Figure 6. [e] $(H_2N)_2CO$; tetragonal system; space group $P\bar{4}2_1m$ (no. 113); $Z = 2$.

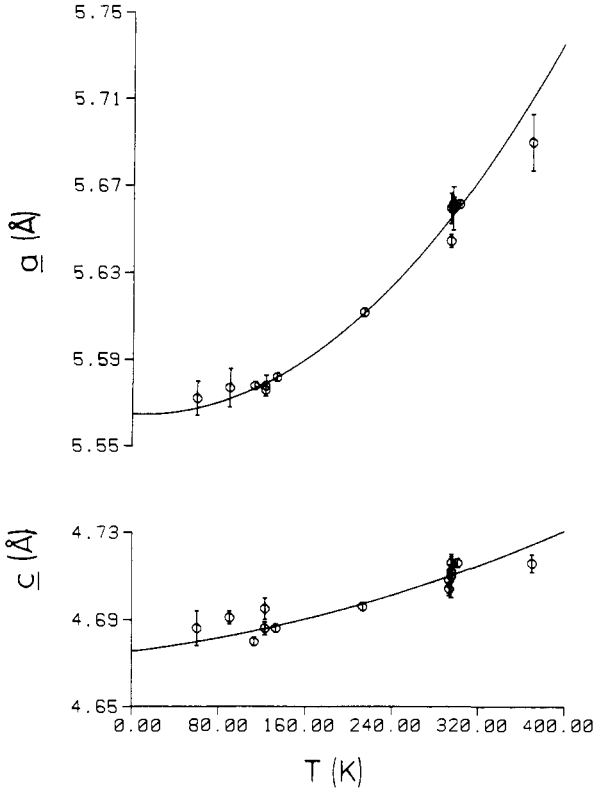


Figure 6. Temperature dependence of the lattice parameters of urea (see also Table IV). The coefficients of the least-squares curves, $a = a_0 + a_1T + a_2T^2$ and $c = c_0 + c_1T + c_2T$, are $a_0 = 5.565$ (12), $a_1 = -1.62 \times 10^{-5}$, $a_2 = 1.12 \times 10^{-6}$, $c_0 = 4.676$ (11), $c_1 = 6.11 \times 10^{-5}$, and $c_2 = 1.92 \times 10^{-7}$.

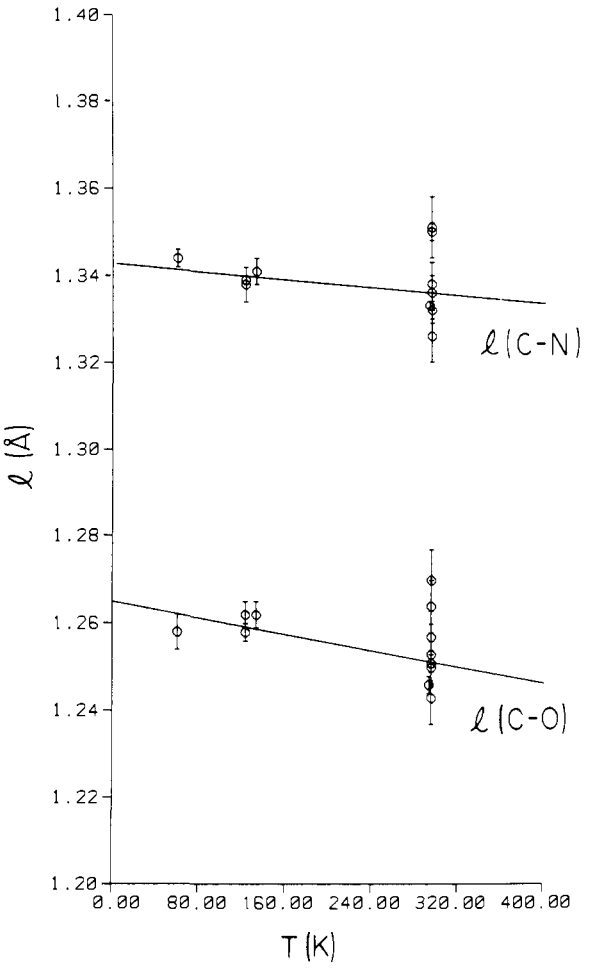


Figure 7. Apparent bond lengths in urea plotted against temperature. (See also Table I. For "room temperature" we assumed $T = 295$ K. The electron diffraction bond lengths reported by Lobachev and Vainstein[52] are not plotted). The correlation statistics for the $n = 12$ C–N bond lengths are $r = -0.21$ and $p(n, |r|) = 0.25$; the equation of the least-squares line is $l = 1.343\ (4) - (2.3 \times 10^{-5})T$. Corresponding values for the C–O bond lengths are $n = 12$, $r = -0.33$, $p(n, |r|) = 0.15$, and $l = 1.265\ (4) - (4.6 \times 10^{-5})T$.

conclude that formation or strengthening of a hydrogen bond to the ureido oxygen of enzyme-bound biotin—from bicarbonate or phosphate or apoenzyme—can assist the binding of an $N^{1\prime}$-carboxyl group by increasing the acidiy of the $N^{1\prime}$-hydrogen atom (cf. **2** and **3**). After translocation, formation of a hydrogen bond to the ureido oxygen of $N^{1\prime}$-carboxybiotin can assist the release of the carboxyl group by withdrawing the $N1'$ lone pair density from the $N^{1\prime}$-carboxyl π system (**6**, **7**).

Appendix

Effects of Temperature and of Atomic Nonsphericity. With increasing temperature, the mean square displacements of atoms vibrating about their mean positions in crystals increase. This is the cause of the thermal expansion of solids. In molecular crystals, most molecular vibrations that do not involve hydrogen atoms are not excited at temperatures below the melting temperature. So with increasing temperature, lattice vibrations and low-frequency molecular bending vibrations become excited and nonbonded intermolecular distances increase, but bond lengths between non-hydrogen atoms should not change.

As indicated in Table I, the crystal structure of urea has been studied at several temperatures. Available data on the thermal

expansion of urea crystals are summarized in Table IV, and plotted in Figure 6 along with quadratic polynomials fitted to the data by least squares. A possible low-temperature phase transition in urea has been reported by Lebioda, Hodorowicz, and Lewinski.[12] They observed temperature-dependent splittings of powder diffraction peaks and an apparent anomaly in the *c* axis thermal expansion at ~190K, but they were not able to interpret these effects in terms of either a change in crystal symmetry or a structural modulation. The observed effects were less noticeable in slowly grown crystals than in rapidly crystallized samples, which would be expected to have a higher density of imperfections that could act as sites for nucleation of a new phase.

Bond lengths for urea from Table I are plotted against temperature in Figure 7. The small decreases in the bond lengths with increasing temperature indicated in Figure 7 are of questionable statistical significance, but they do conform to the well-known phenomenon of shortening of *apparent* bond lengths due to thermal vibrations (see, e.g., ref 13). The distance between the mean positions of two vibrating atoms will always be smaller than the mean of the instantaneous interatomic distances. The amount of the apparent shortening depends on the correlation of the atomic vibrations.

None of the bond lengths listed in Table I is corrected for apparent shortening due to thermal vibration. In several of the studies listed, the original authors reported only bond lengths values that were corrected for thermal vibration, and in those cases we recalculated the bond lengths from the atomic coordinates so that all data would be compared on the same (uncorrected) basis. The effects of both the external lattice vibrations[14] and internal molecular vibrations[15] on the bond lengths in urea have been carefully analyzed by Scheringer,[16] who found that at 293 K the corrections to be added to the C–N and C–O bond lengths are 0.011 and 0.008 Å, respectively. The intercept values for the bond lengths from Figure 7, l(C–N) = 1.343 (4) and l(C–O) = 1.265 (4) Å at T = 0 K, agree very well with the averages of the several sets of vibration-corrected bond lengths reported[16] by Scheringer, $\bar{l}$(C–N) = 1.347 (3) and l(C–O) = 1.259 (4) Å.

The thermal vibration errors in Table I are presumably partly compensated in the case of the X-ray determined C–O bond lengths by atomic nonsphericity errors,[17] which shift the apparent position of the O atom toward its lone pair electrons and thus lengthen the apparent C–O distance. Nonsphericity shifts affect only X-ray results, which give positions of atomic electron density centroids, and not neutron results, which give nuclear positions. Examples of nonsphericity shifts of O atoms toward their lone pairs have been given by Coppens,[17] who found that in cyanuric acid, for example, the C–O bond lengths determined with X-ray data were about 0.005 Å longer than those determined with neutron data.

Overall then, we can expect that the bond lengths in Table I might be too short by 0.003–0.01 Å, but these errors, for the most part, do not exceed the estimated standard deviations given in Table I.

Acknowledgment. This work was greatly aided by the bibliographic compilation "Molecular Structures and Dimensions", edited by O. Kennard, D. G.Watson, F. H. Allen, and S. M. Weeds of the Cambridge Crystallographic Data Centre. I am grateful for very helpful discussions of this work with my colleague, George DeTitta, and for the support of this work by Grant AM19856 from the National Institutes of Health.

Registry No. Biotin, 58-85-5.

(12) Lebioda, L.; Hodorowicz, S.; Lewinski, K. *Phys. Status Solidi A* **1978**, *49*, k27–k30.
(13) Willis, B. T. M.; Pryor, A. W. "Thermal Vibrations in Crystallography"; Cambridge University Press: London, 1975; pp 115 ff, 197 ff.
(14) McKenzie, D. R.; Pryor, A. W. *J. Phys. C* **1971**, *4*, 2304–2312.
(15) Ishii, M.; Scheringer, C. *Acta Crystallogr., Sect. A* **1979**, *A35*, 613–616.
(16) Scheringer, C. *Acta Crystallogr., Sect. A* **1980**, *A36*, 814–818.
(17) Coppens, P. *Acta Crystallogr. Sect. B* **1974**, *B30*, 255–261.