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Amide Group Deformation in Medium-Ring Lactams

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Results of crystal structure analyses of medium-ring lactams and their hydrochloride adducts are surveyed, with particular attention to the deformations of the amide group induced by ring constraints, protonation and interactions with neighbouring atoms. The ring conformations observed for lactams are strikingly similar to those derived from force-field calculations for corresponding cycloolefins. They provide an explanation why multiple N–H stretching frequencies are observed in dilute solutions of some lactams but not of others. Out-of-plane deformations of the amide group are described in terms of twisting (τ) and bending (χ_C, χ_N) coordinates. The structural evidence suggests that the carbonyl end of the amide group has a much greater resistance to out-of-plane bending than the nitrogen end, in agreement with results of vibrational analysis. Some characteristic features of the potential energy surface $V(\tau, \chi_N)$ are delineated and an approximate parametrization of this surface is derived from structural and spectroscopic evidence.

Introduction

Crystal structure studies of medium-ring compounds have provided much of the experimental data required for testing, comparing and parametrizing different kinds of force fields used in molecular mechanics calculations [see Engler, Andose & Schleyer (1973) for a recent paper containing references to earlier work]. Such calculations have furnished, in turn, estimates of structural parameters and strain energies for conformations that are not directly observable, and have contributed, in some cases, to the interpretation of disorder phenomena arising from the presence of more than one conformation at a given site (Dunitz, Eser, Bixon & Lifson, 1967). The important feature of cyclic molecules for structure–energy correlations consists in the special geometric constraints that characterize each ring size. Because of these constraints, structural parameters, such as bond lengths, bond angles and torsion angles, are not free to adopt the strain-free values that occur in open-chain compounds. In the small- and medium-ring range, each ring size presents a special problem of energy minimization. Now that force fields of relatively high quality are available for describing the energy hyperspace of polymethylene chains, structural studies of medium-ring molecules containing other groups should be of interest in indicating how these groups adapt themselves to the different constraints imposed by ring size.

The secondary amide group (Fig. 1) is known to exist preferentially in nearly planar *trans* or *cis* forms, with the former 2–3 kcal mole^{-1} more stable, provided that the alkyl substituents are not too bulky. In small-ring lactams the amide group is necessarily *cis*; it can adopt the more stable *trans* conformation only when the ring is large enough to accommodate a torsion angle of approximately 180° about one of its bonds. From infrared and molecular polarization evidence, Huisgen, Brade, Walz & Glogger (1957) concluded that the crossover point occurs at the nine-membered ring, caprylolactam, which exists as a *trans*-amide in the crystal but as an equilibrium mixture of *cis*- and *trans*-amides, in approximate ratio 4:1, in solution. Model-building suggests that the *trans*-amide group in caprylolactam should be markedly non-planar, as confirmed by infrared studies (Hallam & Jones, 1967).

In order to study the effect of ring size on the structure and, in particular, the planarity of the amide group, we have investigated the series of medium-ring lactams from the seven-membered ring of caprolactam to the twelve-membered ring of undecylolactam. We have completed detailed crystal structure analyses for caprolactam (7), caprylolactam (9) and pelargolactam (10), which has a disordered crystal structure. In addition, to study the corresponding effects of protonation, we have also determined the structures of several crystalline adducts of the lactams with HCl in various proportions. The crystallographic data are summarized in Table 1, and detailed results have been given in a series of accompanying communications (Winkler & Dunitz, 1975*a–i*).

Survey of structural results

Out-of-plane deformation of the amide group

The $3N-6$ coordinates required to specify the relative positions of N atoms may be chosen so that $2N-3$ coordinates lie in a given plane. The remaining $N-3$ coordinates then describe displacements from the given plane. It follows that the out-of-plane deformations of the amide group ($N=6$) can be described in terms of three parameters, which are conveniently chosen as two out-of-plane bending parameters, χ_N and χ_C, and a twisting parameter, τ (Winkler & Dunitz, 1971).

Table 1. *Crystallographic data for lactams* $(CH_2)_{n-2}CONH$ *and adducts with* HCl

Column *R* gives the final *R* value, column *N* the number of reflexions measured.

Compound	*n*	Formula	M.W.	Space group	*a* (Å)	*b* (Å)	*c* (Å)	*α*(°)	*β*(°)	*γ*(°)	*U* (Å³)	*Z*	D_m	D_x	*R*	*N*
Caprolactam	7	$C_6H_{11}NO$	113·16	*C*2/*c*	19·28	7·78	9·57	90	112·39	90	1326·8	8	1·12	1·133	0·048	1017
Caprylolactam	9	$C_8H_{15}NO$	141·21	*Cc*	5·00	23·15	7·21	90	104·76	90	807·6	4	1·16	1·161	0·031	1038
Pelargolactam	10	$C_9H_{17}NO$	155·23	$Pna2_1$	13·71	4·92	13·98	90	90	90	942·9	4	1·10	1·093	–	686
Caprinolactam	11	$C_{10}H_{19}NO$	169·26	*	53·92	53·92	4·93	90	90	120	12419·2	48	1·11	1·086	†	–
Undecylolactam	12	$C_{11}H_{21}NO$	183·29	*Pn*	4·95	13·57	8·69	90	98·75	90	575·0	2	1·07	1·060	†	–
Caprolactam.HCl	7	$C_6H_{11}NO.HCl$	149·62	$Pca2_1$	10·18	10·43	7·61	90	90	90	807·8	4	1·22	1·230	0·052	866
Enantholactam.HCl	8	$C_7H_{13}NO.HCl$	163·64	$P2_1/c$	9·85	6·98	12·44	90	95·96	90	851·1	4	1·28	1·277	0·044	1477
Caprylolactam.HCl	9	$C_8H_{15}NO.HCl$	177·67	$P2_1/c$	12·79	14·88	10·84	90	109·60	90	1943·5	8	1·22	1·214	0·056	2952
Pelargolactam hemi-HCl	10	$(C_9H_{17}NO)_2.HCl$	346·92	$P3_121$	7·26	7·26	32·71	90	90	120	1492·3	3	1·17	1·158	0·039	630
Tripelargolactam oxonium chloride	10	$(C_9H_{17}NO)_3$ $H_2O.HCl$	520·17	$P\bar{1}$	12·26	12·74	12·09	108·06	120·39	81·74	1548·3	2	1·14	1·150	0·096	3289
Caprinolactam hemi-HCl	11	$(C_{10}H_{19}NO)_2.HCl$	374·97	$P4_12_12$	13·45	13·45	11·85	90	90	90	2145·3	4	1·16	1·161	0·037	1373
Undecylolactam hemi-HCl	12	$(C_{11}H_{21}NO)_2HCl$	403·03	$P3_121$	7·81	7·81	32·89	90	90	120	1735·8	3	1·16	1·157	†	–

* Laue symmetry $\bar{3}m$, probably OD-type of structure
† Crystals not investigated further

These parameters can be expressed in terms of the four linearly dependent torsion angles about the C–N bond, $\omega_1=\omega(C_\alpha C'NC_\alpha)$, $\omega_2=(OC'NH)$, $\omega_3=\omega(OC'NC_\alpha)$ and $\omega_4=\omega(C_\alpha C'NH)$, which are related by the condition $(\omega_1+\omega_2)-(\omega_3+\omega_4)=0 \pmod{2\pi}$. The relevant expressions are:

$$\chi_C=\omega_1-\omega_3+\pi=-\omega_2+\omega_4+\pi \pmod{2\pi} \quad (1)$$

$$\chi_N=\omega_2-\omega_3+\pi=-\omega_1+\omega_4+\pi \pmod{2\pi} \quad (2)$$

$$\tau=\tfrac{1}{2}(\omega_1+\omega_2) \quad (3)$$

with the side condition $|\omega_1-\omega_2|<\pi$, which states that a case with $\omega_1=170°$, $\omega_2=-175°$ should be treated as if $\omega_1=170°$, $\omega_2=185°$.

This choice of out-of-plane parameters is similar to one frequently used by spectroscopists for analysing the out-of-plane vibrations of amides. The only difference is that for vibrational analysis the factor of $\frac{1}{2}$ appearing in equation (3) is usually omitted, *i.e.* the twisting parameter is taken as $\tau'=\omega_1+\omega_2=2\tau$. This choice is more convenient for discussing and comparing force constants, since χ_C, χ_N and τ' are now on the same scale, but it has the disadvantage that the distinction between *cisoid* and *transoid* conformations of the amide group is lost.

Table 2 summarizes the values of the out-of-plane parameters found in those analyses where the position of the amide H atom was refined. The values of χ_N and τ are affected by uncertainty in the H positions and are much less reliable than the χ_C values, which are unaffected. The effect of ring constraints should be expressed mainly in the deviation of the ring torsion angle $\omega_1(C_\alpha C'NC_\alpha)$ from 0° or 180° for *cisoid* and *transoid* amide groups, respectively. In all cases except one, this deviation is greater than that of the angles ω_2, ω_3, ω_4. It is a maximum (32°) for the *trans*-amide group in the nine-membered ring and is still appreciable (12°) in the ten-membered ring. Moreover, $\Delta\omega_1$ is always larger than $\Delta\tau$, *i.e.* the net effect of the out-of-plane bends at C′ and N is to reduce the twist angle to a smaller value than it would have in the absence of bending. From equations (1)–(3), ω_1 can be expressed in terms of the out-of-plane parameters χ_C, χ_N and τ:

$$\omega_1=\tau+\tfrac{1}{2}(\chi_C-\chi_N)\,. \quad (4)$$

It is only for the markedly non-planar amide group of caprylolactam that the separate contributions of χ_C, χ_N and τ can be reliably assessed. Table 2 shows that the main contributions come from χ_N (37%) and τ

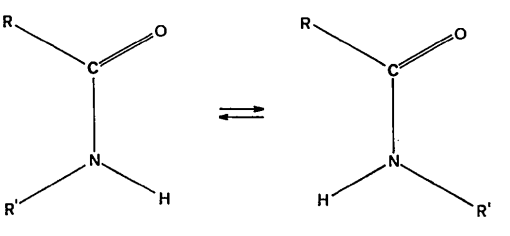


Fig. 1. *cis*- and *trans*-forms of the secondary amide group.

(54%), with χ_C relatively unimportant (9%). In the other cases, the picture is not so clear, partly because it is blurred by the uncertainties in χ_N and τ, partly because the idea of a single dominant constraint is less applicable, and other factors, such as hydrogen bonding, have to be taken into account. The only cases where the contribution of χ_C is more than 20% of ω_1 are in the protonated *cis*-amide groups of enantholactam. HCl and caprylolactam. HCl. There are grounds for believing that the out-of-plane bending at the carbonyl carbon in these structures results more from an electrostatic interaction with a neighbouring chloride ion than from any effect of ring strain (Winkler & Dunitz, 1975*c*,*e*).

Effects of protonation

In all adducts of the medium-ring lactams with HCl, protonation of the amide group occurs at the oxygen atom. For the three monoprotonated *cis*-lactams, an electron density peak of about 0·35 e Å^{-3} occurs about 1 Å distant from the oxygen atom, roughly in the O···Cl$^-$ direction. For the other cases, protonation at oxygen is indicated by the hydrogen-bonding patterns and characteristic changes in the C′–O and C′–N bond lengths. From simple theoretical considerations, it would be expected that protonation at oxygen should be accompanied by an enhancement of the C′⋯N double-bond character, which should shorten the bond length and increase the resistance to the out-of-plane deformations τ and χ_N. Correspondingly, the C′–O bond should become somewhat longer.

Unfortunately, it was not possible to obtain accurate structural parameters for unprotonated and protonated lactams in the same ring conformation. For the seven-membered ring the structure of the unprotonated form could be determined accurately, but the protonated form suffers from disorder. For the eight-membered ring, only the protonated form was studied – enantholactam itself has a low melting point (28 °C) and was not studied. For the nine-membered ring, protonation is accompanied by a drastic change in conformation; the amide group of the unprotonated lactam is *transoid* and highly non-planar, whereas it adopts a more nearly planar *cisoid* conformation in the protonated form. The structures of the unprotonated ten- and eleven-membered rings are disordered: a partial analysis was possible only for the former. The twelve-membered rings were not studied in any detail at all. Although direct comparison of the influence of protonation on the out-of-plane deformations of the amide group under exactly the same geometrical constraints is not possible from our results, the change from highly non-planar *transoid* to nearly planar *cisoid* amide group on protonation of caprylolactam does suggest that out-of-plane deformations are energetically more expensive in protonated than in unprotonated amides.

Table 3 summarizes the bond lengths and angles of the amide group in protonated and unprotonated lactams where the atomic positions involved were not seriously affected by disorder. It is clear that unprotonated caprolactam and caprylolactam show only relatively small differences (< 0·01 Å in bond lengths, < 2·5° in bond angles) from the standard dimensions of the *cis*- and *trans*-peptide unit, respectively, whereas in protonated lactams the C′–O bond tends to become longer, the C′–N bond shorter, as the degree of protonation increases. There are also appreciable changes in the bond angles at C′ in the protonated *cis*-lactams, which show a decrease of 4–6° in NC′O and a similar increase in NC′C$_\alpha$. On the other hand, the C′NC$_\alpha$ angle is hardly affected. The increase in the internal ring angle NC′C$_\alpha$ on going from the unprotonated 7-ring to the protonated 8- and 9-rings is not necessarily due to protonation for it might simply reflect the general trend that bond angles in medium rings tend to be larger than normal in order to lessen the degree of puckering and thus alleviate transannular repulsive interactions – the mean internal bond angle increases from 116·3° in the 7-ring, to 116·9° in the 8-ring, to 117·8° in the 9-ring. However, the observed *difference* between the two ring angles, C′NC$_\alpha$ and NC′C$_\alpha$ is 7° in the unprotonated amide and only 2–3° in the protonated ones, suggesting that protonation does tend to increase the latter angle. In *N*-methylthiocaprylolactam (Flippen, 1972), with a conformation closely resembling that of protonated caprylolactam, the changes in NC′S and NC′C$_\alpha$ from standard values are in the same sense as those observed here although much smaller. For the *trans*-amide groups the changes in bond lengths and angles on partial protonation are

Table 2. *Out-of-plane deformation parameters* (°) *with e.s.d.'s in parentheses*

E.s.d.'s have been estimated by inserting averaged positional e.s.d. for the C, N and O atoms ($\bar{\sigma}$) and a separate e.s.d. (typically about ten times larger) for the H atom (σ_H) into expressions for the s.d. of a torsion angle (Huber, 1961; Stanford & Waser, 1972) assuming standard dimensions of the amide group (Marsh & Donohue, 1967). The following approximate expressions are applicable (χ_C, χ_N, τ in rad.): $\sigma^2(\chi_C) \sim 9\bar{\sigma}^2$, $\sigma^2(\chi_N) \sim 9\bar{\sigma}^2 + 1{\cdot}4\ \sigma_H^2$, $\sigma^2(\tau) \sim 2\bar{\sigma}^2 + 1{\cdot}5\ \sigma_H^2$.

cis-Amide groups	*n*	χ_C	χ_N	τ	ω_1	ω_2	ω_3	ω_4
Caprolactam	7	0·8 (0·4)	−6·5 (3·0)	0·6 (1·5)	4·2	−3·1	−176·6	177·7
Enantholactam.HCl	8	4·4 (0·5)	−1·6 (3·0)	2·6 (1·5)	5·6	−0·4	−178·8	−176·0
Caprylolactam.HCl	9	4·1 (0·6)	2·3 (3·0)	8·3 (1·5)	9·2	7·4	−174·9	−168·5
		4·0 (0·6)	−6·4 (4·0)	4·3 (2·0)	9·5	−0·9	−174·5	−176·9
trans-Amide groups								
Caprylolactam	9	−5·8 (0·5)	23·1 (2·2)	162·9 (1·1)	148·4	177·3	−25·8	−8·5
Pelargolactam hemi-HCl	10	−1·0 (1·2)	12·7 (5·0)	175·2 (2·5)	168·3	−177·8	−10·7	1·2
Caprinolactam hemi-HCl	11	−1·4 (0·5)	9·7 (3·0)	180·0 (1·5)	174·5	−174·5	−4·1	4·2

not so pronounced as for the fully protonated *cis*-amide groups.

The standard dimensions of the *trans*- and *cis*-peptide units (Marsh & Donohue, 1967; Ramachandran & Sasisekharan, 1968) have been obtained by averaging results of selected crystal structure analyses. Hydrogen bonding to the oxygen atom of the amide group is a characteristic feature of these crystal structures, and the approach of the hydrogen atom to the oxygen in such cases can be regarded as a kind of incipient protonation that could lead to slight changes in the dimensions of the amide group with respect to those of the free molecule. The only amide for which structural data are available for the gas-phase molecule is formamide. According to the latest microwave study of this compound (Hirota, Sugisaki, Nielsen & Sørensen, 1974) the C–O and C–N distances are 1·219 (12) and 1·352 (12) Å respectively and the O–C–N angle is 124·7 (3)°, values that are markedly different from those obtained for formamide in the crystalline state (Ladell & Post, 1954) – 1·255 Å (C–O), 1·30 Å (C–N) and 121·5° (O–C–N). The parameters obtained in earlier microwave investigations (Kurland & Wilson, 1957; Costain & Dowland, 1961) differ somewhat from those reported by Hirota *et al.* but they show the same kind of deviations – shorter C–O distance, longer C–N distance and larger O–C–N angle – compared with the solid-state values.*

From the observed trends in d(C′–O), d(C′–N) and α(N–C′–O) with increasing degree of protonation, the effective degree of protonation of the standard amide group is estimated to be 15–20% (Fig. 2).

Ring conformations and conformational equilibria

For caprolactam, the same chair-like ring conformation of the seven-membered ring, with an approximate mirror-plane passing through the centre of

* *Note added in proof*: – This was written before we became aware of new electron-diffraction results for gaseous formamide, *N*-methylformamide, acetamide and *N*-methylacetamide (Kitano & Kuchitsu, 1973, 1974; Kitano, Fukuyama & Kuchitsu, 1973). The differences between gas-phase and solid-state values for the C′–N and C′–O distances are all in the same sense as described in the text. However, the OC′N angle in gaseous *N*-methylacetamide [121·8(4)°], taken together with our results (Fig. 2, Table 3), suggests that the value adopted for this angle in the 'standard' peptide group (123·5°) may be slightly too large.

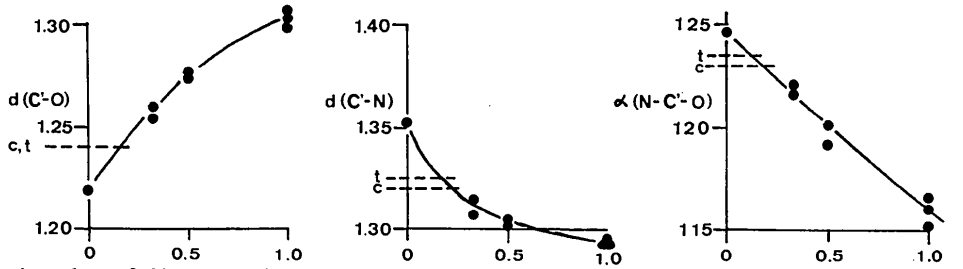


Fig. 2. Correlation plots of C′–O and C′–N bond lengths and of N–C′–O angle against degree of protonation of amide group. The corresponding dimensions in the standard *cis*- and *trans*-amide are shown by dashed lines.

Table 3. *Values of selected bond lengths (in* Å*) and bond angles (in degrees) of amide group as observed in lactams and their adducts with* HCl *(e.s.d.'s in parentheses)*

cis

	Unprotonated		Protonated	
	Standard[a]	Caprolactam	Enantholactam.HCl	Caprylolactam.HCl
C′–O	1·24	1·242 (2)	1·307 (3)	1·299 (4) 1·303 (4)
C′–N	1·32	1·327 (2)	1·293 (3)	1·293 (3) 1·295 (3)
N–C′–O	123	120·9 (2)	116·6 (2)	115·2 (3) 116·0 (3)
N–C′–C_α	118	118·5 (2)	122·8 (2)	124·1 (3) 124·0 (3)
O–C′–C_α	119	120·6 (2)	120·4 (2)	120·6 (3) 119·9 (3)
C′–N–C_α	126	125·5 (2)	125·3 (2)	127·3 (3) 126·8 (3)

trans

	Unprotonated		½ Protonated		½ Protonated	
	Standard[b]	Caprylolactam	Tripelargolactam H_3O.Cl		Pelargolactam-hHCl	Caprinolactam-hHCl
C′–O	1·24	1·233 (2)	1·254 (8)	1·260 (7)	1·277 (6)	1·275 (3)
C′–N	$1{\cdot}32_5$	1·334 (3)	1·307 (7)	1·315 (7)	1·305 (8)	1·302 (3)
N–C′–O	123·5	122·4 (2)	121·6 (7)	122·1 (6)	120·1 (6)	119·2 (2)
N–C′–C_α	116·0	115·0 (5)	115·8 (7)	115·3 (6)	116·8 (6)	120·0 (2)
O–C′–C_α	120·5	122·3 (2)	122·6 (7)	122·6 (6)	123·1 (6)	120·9 (2)
C′–N–C_α	122·0	122·8 (2)	122·6 (7)	122·4 (7)	123·7 (6)	123·0 (2)

(*a*) Standard values for *cis*-peptide unit as given by Ramachandran & Sasisekharan (1968).
(*b*) Standard values for *trans*-peptide unit as given by Marsh & Donohue (1967).

the C′–N bond and the opposite CH_2 group, is observed in both protonated and unprotonated forms.

The ring conformation of the protonated enantholactam molecule is similar to that observed in other eight-membered rings containing a more or less rigid synplanar bond (Trefonas & Majeste, 1963; Cameron, Cheung, Ferguson & Robertson, 1965). Several energy minimization calculations with various force fields (Favini, Buemi & Raimondi, 1968; Allinger & Sprague, 1972; Ermer & Lifson, 1973) show that for *cis*-cyclooctene, the same type of conformation is favoured by several kcal mole^{-1} over any of its competitors. It seems very likely that this type of ring conformation is also the preferred one for the unprotonated enantholactam molecule.

In the crystalline state caprylolactam adopts a ring conformation with an approximate twofold rotation axis passing through the centre of the C′–N bond and the opposite CH_2 group; the amide group is *transoid* and decidedly non-planar (Table 2). As mentioned in the Introduction, this is not the preferred conformation in solution, where the major species in the 4:1 equilibrium mixture has a *cisoid* amide group. We can assume that the conformation present in solution is very similar to that observed in the crystalline adduct with HCl. The relative stabilization of the *transoid* form in the crystal can be attributed to the energetically more favourable hydrogen-bonding pattern that can be attained (Winkler & Dunitz, 1975*d*).

The ring conformations observed for the partially protonated pelargolactam molecule in two crystalline adducts (Table 1) are virtually the same, with a *transoid* amide group. This conformation is not related to what is believed to be the preferred conformation of *trans*-cyclodecene (Ermer & Lifson, 1973), but the cycloolefin has at least five other conformations within a 2·5 kcal mole^{-1} enthalpy range and one of these corresponds closely to the one found here. This conformation also gives a good but not perfect fit to the electron density observed for the disordered structure of pelargolactam itself.

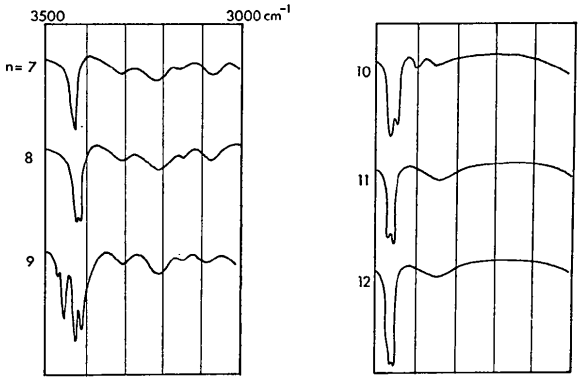


Fig. 3. Splitting of N–H absorption bands in the infrared spectra of medium-ring lactams in dilute chloroform solution, redrawn from Hallam & Jones (1967).

Ermer & Lifson (1973) and Ermer (1973) have carried out energy minimization calculations with their consistent force field for many conformations of medium-ring cycloolefins, including all the types of conformation found for the lactams and their HCl adducts. Detailed comparisons of the torsion angles calculated for the cycloolefins and observed for the lactams are given in the accompanying communications (Winkler & Dunitz, 1975 *b–e, g, i*). The agreement is good in all cases and excellent for the monoprotonated *cis*-lactams.

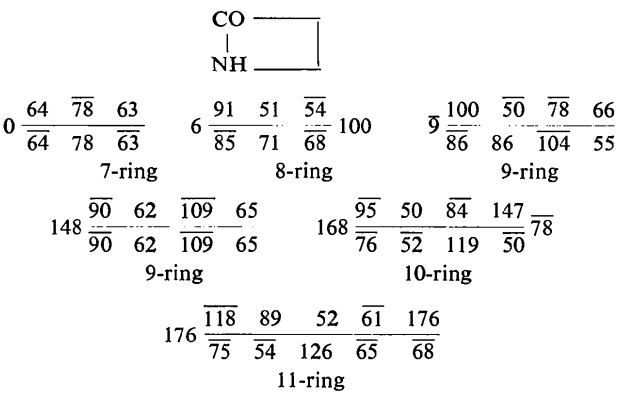
It may seem remarkable that a force field parametrized to describe the behaviour of olefins should reproduce the observed structures of amides so well. The amide group has a far lower rotation barrier than the C=C double bond and a far lower resistance to out-of-plane bending at one of its ends (the >NH grouping), apart from other differences in equilibrium parameters and flexibility. Nevertheless, in comparison with the highly flexible polymethylene segments of the rings it can be regarded, like the >C=C< grouping, as a fairly planar system, and this resemblance seems enough to produce a general similarity between the conformations of lactams and cycloolefins. The overall good agreement, in particular, the agreement between the observed torsion angle round the C–N bond of the markedly non-planar amide group in caprylolactam (148·5°) and the calculated torsion angle round the C=C bond of *trans*-cyclononene, suggests, moreover, that the ring constraints operative in a given ring-size are more effective in determining the molecular conformation than the details of the force field. The excellent agreement obtained for the protonated *cis*-lactams shows that the protonated amide group mimics the double bond even better than the unprotonated does. This can be attributed to (1) the enhanced double-bond character of the C–N bond in protonated species, (2) the smaller difference between the $C_\alpha NC'$ and $NC'C_\alpha$ angles in protonated species (Table 3).

Table 4 shows the patterns of torsion angles (in some cases somewhat idealized) observed in the series of medium-ring lactams and their protonated adducts. If the asymmetry of the amide group is disregarded for the moment, the pattern for the *cis*-7-ring shows the mirror symmetry of the idealized conformation, which is quite close to those actually observed. Similarly, the pattern for the *trans*-9-ring shows a dyad axis. The calculated conformations of the corresponding cycloolefins (Ermer & Lifson, 1973) show perfect *m* and C_2 symmetry respectively. For these two cases, formal interchange of the CO and NH ends of the amide group, preserving the same torsion-angle pattern, leads to conformations that are identical to or enantiomorphic with the original ones.

The other conformations described in Table 4 have no non-trivial symmetry elements, nor do those of the corresponding cycloolefins. For these cases, interchange of the CO and NH ends of the amide group leads to a different conformation but to one so closely

Table 4. *Torsion angle patterns (in some cases somewhat idealized) of medium-ring lactams*

The number given at the left of each cyclic sequence is the angle round the C′–N bond.



related to the original that it cannot differ much in strain energy.

The observation of multiple bands for the N–H stretching mode of medium-ring lactams in dilute CCl_4 solutions has been interpreted as evidence for the existence of conformational equilibria (Luck, 1965; Hallam & Jones, 1967; Chen & Swenson, 1969), although the nature of the species involved has remained rather obscure. Fig. 3, redrawn from Hallam & Jones (1967), shows the observed infrared spectra. *trans*-Amides absorb in the range 3440–3470 cm^{-1}, *cis*-amides in the range 3400–3430 cm^{-1}. Caprylolactam absorbs in both regions, and pelargolactam shows a weak band in the *cis*-range besides its main band in the *trans*-range. Otherwise the bands lie clearly in either the *cis* or *trans* regions. With the exception of caprolactam, all the bands are split into doublets separated by 8–20 cm^{-1}. Spectra of *N*-deuterated lactams show that Fermi resonance is not responsible for the observed splittings (Swenson & Chen, 1973), which are also present in the spectra of thio- and selenolactams (Hallam & Jones, 1969).

It seems plausible to assume that the conformations observed in this series of crystal structure studies (Table 4) are also present in solution. The doublets found in the solution spectra of enantholactam (8-ring), caprylolactam (9-ring, *cis*-band), pelargolactam (10-ring) and caprinolactam (11-ring) indicate the presence of a second conformation with almost the same free energy, which could well be the one derived by interchanging the CO and NH ends of the amide group. For the symmetrical ring skeletons of caprolactam (7-ring) and caprylolactam (9-ring, *trans*) this interchange does not lead to a new conformation so no splitting can arise from it. The N–H band of caprolactam is indeed a singlet, and the doublet in the *trans* band of caprylolactam is the only case where the two intensities differ appreciably. Presumably the minor component is due to some other conformation. X-ray evidence points to a number of rather ill-defined conformations for *trans*-cyclodecene (Dunitz, 1971), and Ermer & Lifson (1973) find at least six that do not differ by more than 2·5 kcal $mole^{-1}$ in enthalpy. Hallam & Jones (1967) report weak shoulders on the high frequency side of the N–H doublet for pelargolactam and for undecylolactam (12-ring), which could indicate that other minor conformations may be present in solutions of these compounds.

There remains the question why the N–H stretching frequency of two conformations related by interchanging the CO and NH ends of the amide group should differ by 10–20 cm^{-1} when differences between bands of different lactams amount only to about 5 cm^{-1}. The interchange leaves the relative positions of the α-carbons invariant and leads to only minor changes in the positions of the β-carbons as well, since the torsion angles about the C′–C_α and N–C_α bonds in the observed conformations do not differ very much (only 5° in the 8-ring).

Smoliková, Havel, Vašičková, Vitek, Svoboda & Bláha (1974) have recently suggested that the N–H splittings for the nine-, ten- and eleven-membered rings are due to the presence of conformational isomers that differ with respect to the N–C_α torsion angle. This would be compatible with our assumption that the relevant conformers are related by simply interchanging the CO and NH ends of the amide group provided that the torsion angles round N–C_α and C′–C_α were appreciably different. Table 4 shows that this is the case only for the eleven-membered ring. For the ten-membered ring, as mentioned above, conformations other than the one observed may be present in solution, and some of these might possibly show larger differences between the two torsion angles. However, it seems very difficult to reconcile the proposal of Smoliková *et al.* with the near equality of these angles in related conformations of the eight- and nine-membered *cis*-lactams. Examination of models suggests that there are no reasonable conformations of the 8- and 9-ring lactams in which torsion angles differ by as much as 60°.

Fig. 4 shows stereoscopic views of the four observed conformations that do not contain any approximate symmetry in their ring skeletons. The two *cis*-lactams show sequences of similar torsion angles, and so do the two *trans*-lactams. In all four conformations, a methylene hydrogen comes much closer to C′ than to N; the *trans*-annular H···C′ distances are 2·5–2·7 Å, and the H atom is above the plane of the amide group, roughly where the π-orbital of the carbon atom should protrude. Interchange of the C′ and N ends of the amide group would put the H atom roughly in the region of the π-orbital of N, and this is the situation in the structure found by Flippen (1972) for *N*-methylthiocaprylolactam. The preference for one form over the other can hardly be very strong, and we might expect both forms to be present in solution equilibrium

in approximately equal amounts. We suggest that it should be more profitable to seek the origin of the N–H band splitting in interactions such as these, rather than in a dependence on the N–C_α torsion angle. However, it must be admitted that the influence of these H···C′ and H···N interactions on the N–H stretching frequency remains obscure.

Packings

Detailed discussions with packing diagrams for the individual crystal structures are given in the accompanying communications (Winkler & Dunitz, 1975*a–i*).

In all nine crystal structures hydrogen bonds are prominent features of the intermolecular association

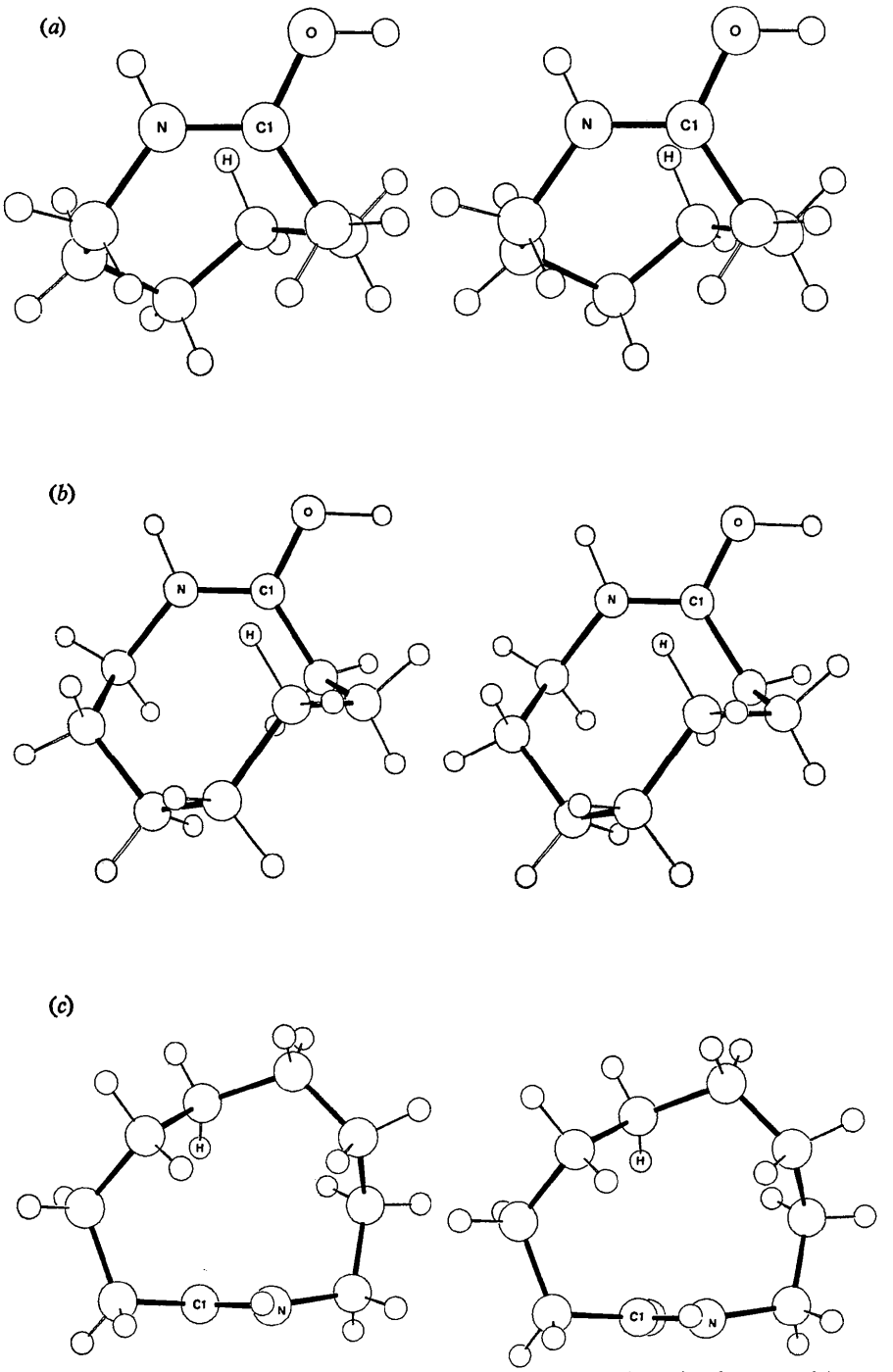


Fig. 4. Stereoscopic views (Johnson, 1965) of observed conformations for four medium-ring lactams: (*a*) enantholactam (protonated), (*b*) *cis*-caprylolactam (protonated), (*c*) pelargolactam.

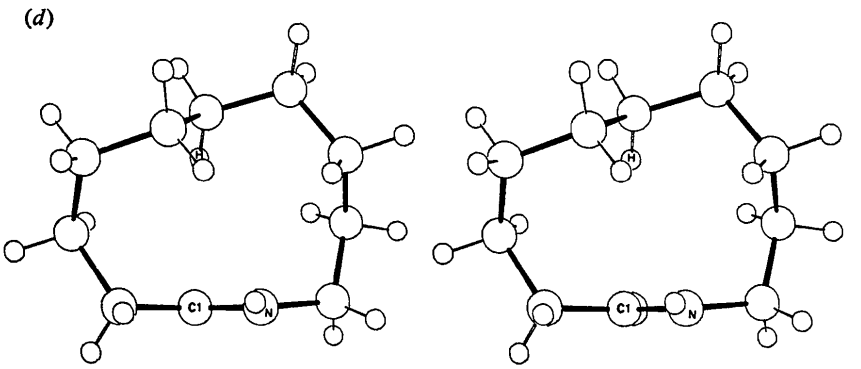


Fig. 4 (*cont.*) (*d*) caprinolactam.

patterns. Caprolactam with its *cis*-amide group forms dimers linked by two NH···O=C bridges, whereas caprylolactam and higher members of the series with *transoid* amide groups form infinite chains in which neighbouring molecules are related by a characteristic translation of 4·9–5·0 Å (Table 1). These basic structural units, dimers or chains, then associate by van der Waals attractions into three-dimensional aggegrates. It is interesting that both lactams with ordered crystal structures have conformations with approximately symmetrical ring skeletons. The occurrence of disordered crystal structures for pelargolactam, caprinolactam and probably also undecylolactam does not seem surprising in view of the expectation that at least two approximately equi-energetic conformations are likely for these molecules (see Fig. 3 and previous discussion).

The crystalline hydrochlorides of the three *cis*-lactams all show $NH\cdots Cl^-$ (3·12–3·20 Å) and $OH\cdots Cl^-$ (2·86–2·92 Å) hydrogen bonds, leading to approximately linear, one-dimensional chains built from alternating protonated amide cations and chloride anions. Such chains can be folded in a number of ways to give a regular, periodic pattern, and the patterns that are actually found can be described as zigzag chain (7-HCl), straight chain (8-HCl) and helix (9-HCl), corresponding to the operations of a glide plane, translation and twofold screw axis, respectively. Electrostatic interactions between anions and cations of different chains seem to be most important for caprolactam hydrochloride, where chloride anions sit above and below the plane of the protonated amide groups, thus linking the zigzag chains into two-dimensional layers. For the larger rings the chloride ions can approach the protonated *cis*-amide cations only from one side, the other being blocked by the intruding polymethylene chain (Fig. 3).

In the two hemihydrochlorides, pairs of lactam molecules are linked by short, symmetrical hydrogen bonds ($O\cdots H^+\cdots O$, 2·43 Å) to form protonated dimers centred on twofold rotation axes [see Speakman (1972) for an extensive review of short, symmetrical hydrogen bonds, mostly in $(O\cdots H\cdots O)^-$ systems]. The chloride anions, also on twofold rotation axes, link the dimeric units into one-dimensional chains

$$[HN.CO\cdots H^+\cdots OC.NH]\cdots Cl^-\cdots [HN.CO\cdots H^+\cdots OC.NH]$$

by hydrogen bonds to two amide nitrogens. Again the resulting sequence of alternating cationic and anionic units can be folded in different ways. Whereas straight chains, pairwise associated by electrostatic interactions, are found in caprinolactam hydrochloride, a helical arrangement with no obvious electrostatic interactions either within or between individual helices is preferred in pelargolactam hydrochloride.

In tripelargolactam oxonium chloride, each oxonium cation forms three very short hydrogen bonds (2·41–2·47 Å) to amide oxygens, and each chloride anion forms three hydrogen bonds to amide nitrogens, leading to the formation of layers with approximate trigonal symmetry. Electrostatic interactions between H_3O^+ cations and Cl^- anions then leads to double layers with non-polar outer surfaces that interact only weakly through van der Waals attractions.

In summary, in all cases hydrogen bonding leads to a characteristic kind of association into structural units (dimers, chains, helices, layers). In the hydrochloride adducts electrostatic interactions between cations and anions do not seem to play the dominating role that might have been expected for them. At most, they influence the secondary association of the hydrogen-bonded units into larger aggegrates.

The torsion angles φ and ψ

The conformation of a polypeptide chain is usually described by the sequence of torsion angles φ_i, χ_i, and ω_i, as defined in Fig. 5. For conformational energy calculations of polypeptides and amides (Brant & Flory, 1965; Scott & Scheraga, 1966; Ramachandran & Sasisekharan, 1968; Levitt & Lifson, 1969; Warshel, Levitt & Lifson, 1970) rotation about the $N\text{–}C_\alpha$ (φ) and $C_\alpha C'$ (ψ) bonds is usually taken into account by introducing threefold cosine potentials. The barriers assumed range from 0·6 to 3·0 kcal mole^{-1} for φ and

from 0·2 to 1·4 kcal mole^{-1} for ψ. There is also disagreement about the positions of the maxima and minima of the φ and ψ potentials, although the majority of quantum chemical calculations for *trans*-amides indicate that the minima occur (Fig. 6) when C_α–R eclipses C′–O ($\psi = \pm 60°$, 180°) and C_α–R′ eclipses N–C′ ($\varphi = 0°$, $\pm 120°$). For *cis*-amides the minima of the φ potential seem to be displaced by 60° ($\varphi = \pm 60°$, 180°) according to calculations by Shipman & Christoffersen (1973), which also indicate that the ψ barrier is larger than the φ barrier in both *cis*- and *trans*-amides.

Table 5 compares values of the torsion angles φ and ψ observed in the series of medium-ring lactams and protonated adducts with the corresponding angles calculated by Ermer & Lifson (1973) for the cycloolefin series. The force field used in the calculations includes a threefold cosine potential with a barrier of 2·5 kcal mole^{-1} and minima at torsion angles of 0, $\pm 120°$ for rotation about the =CH–CH_2 bonds. From the excellent overall agreement between observed and calculated torsion angles one might jump to the conclusion that the φ and ψ potentials must be very similar to this, but it must be kept in mind that the torsion angle patterns in these medium-ring compounds are strongly influenced by ring closure conditions and are not so sensitive to details of the force field. Table 5 shows that for the ring-skeletons where the two torsion angles are not symmetry equivalent, φ takes up the value closer to 60°, ψ the value closer to 120°, whereas we might have expected the reverse, especially in the *trans*-amides. However, the lactams in question are fully or partially protonated. In the two unprotonated lactams with symmetrical ring skeletons ψ is slightly closer to 60° than φ, as expected, but the differences are very small indeed. Since the conformations with values of φ and ψ interchanged occur in solution equilibria in comparable amounts the energies associated with different φ, ψ values 60°, 120° and 120°, 60° must be nearly equal. Depending on the true positions of the minima and maxima of the corresponding potentials, this would imply that (*a*) both barriers are very low, or (*b*) both barriers are of similar magnitude.

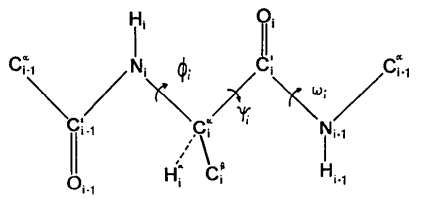


Fig. 5. Definition of torsion angles φ_i, ω_i and ψ_i in polypeptide chain.

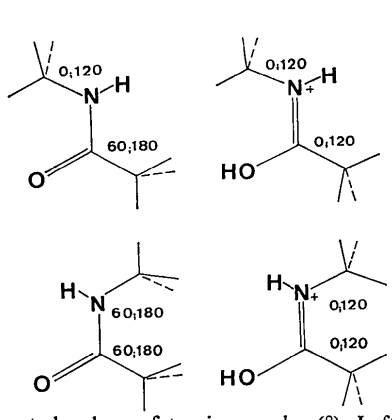


Fig. 6. Expected values of torsion angles (°). Left, unprotonated *cis*- and *trans*-amides, according to Shipman & Christoffersen (1973). Right, fully protonated *cis*- and *trans*-amides, according to bent-bond model.

Table 5. *Values of φ and ψ observed in medium-ring lactams and protonated adducts, with values calculated by Ermer & Lifson* (1973) *for the corresponding cycloolefins (in parentheses)*

Ring size	Compound	φ	ψ
7	Caprolactam	68 (59)	63 (59)
7	Caprolactam.HCl	63 (59)	63 (59)
8	Enantholactam.HCl	85 (83)	91 (91)
9	Caprylolactam	91 (89)	89 (89)
9	Caprylolactam HCl	86 (85)	100 (102)
10	Pelargolactam.h HCl	76 (82)	95 (96)
11	Caprinolactam.h HCl	75 (71)	118 (117)

In a previous section we have shown that considerable changes in bond length and angle occur on full or partial protonation of the amide group, changes that correspond to an increase in the double-bond character of the C′–N bond and a decrease in the double-bond character of the C=O bond. It is very likely that changes in the φ and ψ barriers also occur on protonation, but they do not seem to have been studied. The bent-bond model of the double bond leads to correct predictions of the preferred conformations of carboxylic acids and esters (Dunitz & Strickler, 1968) and it may serve as a guide in the present case. It would suggest (Fig. 6) that, with increasing degree of protonation, the tendency for C_α–R to eclipse C=O becomes less pronounced and may even go over to a preference for C_α–R to eclipse C′···N ($\psi = 0$, $\pm 120°$). At the other end of the amide group any tendency for C_α–R to eclipse N···C′ should become more pronounced ($\psi = 0$, $\pm 120°$). The C′···N bond in the fully protonated amide group should thus simulate the C=C double bond much better than the unprotonated, but for intermediate degrees of protonation the ψ barrier in both *cis*- and *trans*-amides and the φ barrier in *cis*-amides may become virtually zero.

Non-planar amide groups

In the remainder of this paper we try to derive the approximate form of the potential energy surface describing the out-of-plane deformations of the amide group from structural and spectroscopic data obtained for a wide variety of compounds. For this purpose we have to assume that characteristic features of the potential surface are transferable among different amides; in other words, we regard the substituent and hydrogen-

bonding patterns as relatively minor perturbations which can be superimposed on the potential surface without changing its general features. This kind of approach has recently been exploited to derive minimum energy paths from structural data alone for deformations of other sub-systems of chemical interest (Bürgi, 1973; Bürgi, Dunitz & Shefter, 1973, 1974; Muetterties & Guggenberger, 1974).

Table 6 lists values of the out-of-plane deformation parameters τ', χ_N and χ_C observed in various secondary amides with significantly non-planar amide groups. The contribution of χ_C is clearly much less than that of the other two components but, apart from this, no obvious correlation is to be found.

The largest out-of-plane deformation occurs for caprylolactam, where the torsion angle $\omega(C_\alpha C'-NC_\alpha)$ is virtually the same as that calculated for the corresponding angle $\omega(C_\alpha C{=}CC_\alpha)$ in *trans*-cyclononene (150°), in spite of the much greater resistance of the >C=C< grouping to out-of-plane deformation. It seems safe to infer that this angle is largely determined by the geometric constraints effective in the nine-membered ring; to a first approximation we can regard it as being *fixed* by these constraints. Assume that the potential function for out-of-plane deformation is given by a sum of quadratic terms in τ', χ_N and χ_C with no cross terms:

$$2V = c_1\tau'^2 + c_2\chi_N^2 + c_3\chi_C^2 . \qquad (5)$$

Minimization of V with respect to τ', χ_N, χ_C under the constraint

$$2\omega(C_\alpha C'-NC_\alpha) = \tau' + \chi_C - \chi_N = \text{constant} \qquad (6)$$

leads to the relationships $c_1\tau' = c_2\chi_N = c_3\chi_C$. In other words, the relative contributions of twisting and out-of-plane bending to the amide torsion angle (assumed fixed) should be inversely proportional to the quadratic potential constants in (5). From the values given in Table 6 we obtain $c_1 : c_2 : c_3 = 1 : 1{\cdot}5 : 6$. The carbonyl end of the amide group thus seems to have a much higher resistance to out-of-plane bending than the nitrogen end. For the open-chain molecules included in Table 6, the assumption of a single dominating constraint on the amide torsion angle is clearly invalid.

In Table 7 we have assembled values of force constants for out-of-plane vibrations of simple open-chain amides derived from vibrational analyses of infrared and Raman spectroscopic data. Several different kinds of internal and symmetry coordinates were used in these analyses, but for convenience we have expressed all the force constants in terms of τ', χ_C and χ_N by applying appropriate transformations. The corresponding potential energy expression is

$$2V = c_{11}\tau'^2 + c_{22}\chi_N^2 + c_{33}\chi_C^2 + 2c_{12}\tau'\chi_N + 2c_{13}\tau'\chi_C + 2c_{23}\chi_N\chi_C \qquad (7)$$

with τ', χ_N, χ_C in radians. At first sight the agreement between force constants in different amides is so poor

Table 6. *Out-of-plane deformation parameters (in degrees) observed in crystal structures of secondary amides and peptides*

		τ'	χ_N	χ_C	E.s.d.*	References
(*a*)	Perdeutero-α-gly-gly	12·0	8·1	3·3	0·5	Freeman, Paul & Sabine (1970)
(*b*)	Gly-gly.HCl.H_2O	−7·6	−3·6	−2·4	1·0	†
(*c*)	Caprylolactam	−34·2	23·1	−5·8	2·2	Winkler & Dunitz (1975*d*)
(*d*)	Pelargolactam hemi-HCl	9·6	−12·7	1·0	5·0	Winkler & Dunitz (1975*g*)
(*e*)	*N*-Acetyl-L-phenylalanyl-L-tyrosine	−17·8	11·5	−6·3	1·5	Stenkamp & Jensen (1973)
(*f*)	Gly-gly phosphate monohydrate	−19·6	−10·4	0·1	3·0	Freeman, Hearn & Bugg (1972)
(*g*)	Gly-L-leu	1·1	24·1	0·2	3·5	†
(*h*)	L-ala-ala	−10·9	−3·9	−1·6	3·5	†
(*i*)	L-ala-gly	−7·7	2·5	−2·0	3·0	†
(*j*)	Gly-L-ala.HCl	−8·7	17·2	4·5	3·5	†
(*k*)	Acetyl-L-pro-L-methylamide	−6·7	11·4	1·3	3·5	†
(*l*)	L-ala-ala.HCl	−16·8	−21·1	−2·7	6·0	†

* E.s.d's have been calculated as described in Table 2; (*a*), (*b*): neutron diffraction analysis (e.s.d.'s for τ', χ_N and χ_C have same order of magnitude). (*c*)–(*l*): X-ray analysis (e.s.d. refers to τ' and χ_N; for χ_C it is about four times smaller).

† The values have been transferred from a table given by Ramachandran & Koleskar (1973).

Table 7. *Force constants (in* kcal $mole^{-1}$ rad^{-2}*) for out-of-plane vibrations of amide group derived from vibrational analysis of spectroscopic data*

		c_{11}	c_{22}	c_{33}	c_{12}	c_{13}	c_{23}	
(*a*)	*N*-Methylacetamide	24·1	8·6	62·6	−1·7	8·7	−3·3	(1) Jakes & Krimm (1971)
(*b*)	*N*-Methylacetamide	11·9	13·3	20·0	−0·5	−5·3	0·5	(2) Warshel, Levitt & Lifson (1970)
	N-Methylformamide							
(*c*)	*N*-Methylacetamide	6·9	–	54·0	–	–	–	(1) Miyazawa (1961)
	N-Methylformamide	7·2	–	57·2	–	–	–	
(*d*)	*N*-Methylformamide	13·7	17·2	47·2	0	−4·1	−0·8	(1) Suzuki (1962)
(*e*)	Acetamide	20·0	12·8	55·0	−0·9	2·3	−3·3	Uno, Machida & Saito (1971)

(1) The bending parameters used in these analyses have been expressed in terms of χ_N and χ_C, assuming bond angles of 120° at C' and N.

(2) For conversion of force constants the cosine potentials $V(\omega_i) = V_2(i)\,(1-\cos 2\omega_i)/2$ have been approximated by $V(\omega) = 2V_2\omega_i^2$.

that one might well be tempted to abandon any ideas about transferability. However, some of the worst inconsistencies (*a–d*) come from analyses of spectra of the same compounds (*N*-methylacetamide and *N*-methylformamide) but with different force fields!

With one exception (*b*) the c_{33} values cluster around 55 kcal mole^{-1} rad^{-2} and are clearly larger than the other two diagonal force constants. The value of 20 kcal mole^{-1} rad^{-2} is clearly too low, and inspection of the corresponding calculated frequencies for *N*-methylformamide and its deuterated analogues shows that they are systematically too low by about 10%.

Values for c_{11} and c_{22} are much lower than those of c_{33} (in qualitative agreement with the ratios estimated above). The two lowest values of c_{11} come from an investigation (*c*) where a complete normal coordinate analysis was not carried out (χ_N neglected) and can be passed over. The value of 11·9 kcal mole^{-1} rad^{-2} from analysis (*b*) is also probably too low since the calculated frequencies for the amide VII band (main torsional contribution) in *N*-methylacetamide and deuterated analogues are all about 25% too low. We mention elsewhere (Winkler & Dunitz, 1975*a*) that the force field assumed in (*b*) also leads to unsatisfactory agreement between observed and calculated structural parameters for caprolactam. The remaining values of c_{11} (*a,d,e*) range from 13–24 kcal mole^{-1} rad^{-2}, those of c_{22} from 9–17 kcal mole^{-1} rad^{-2}.

It has often been assumed that the *cis–trans* isomerization process in amides consists of a pure twisting round the C′–N bond described by a potential of the form

$$V(\omega)=\frac{V_B}{2}(1-\cos 2\omega)=\frac{V_B}{2}(1-\cos\tau'). \qquad (8)$$

The curvature at $\omega=0$ can be identified with the quadratic force constant c_{11}, leading to $V_B=2c_{11}$. From the estimates given above, the barrier to isomerization would then be expected to lie in the range 25–50 kcal mole^{-1}. Activation energies derived from n.m.r. spectroscopic data are typically somewhat lower than this, the best estimates being 18–19 kcal mole^{-1} for *N,N*-dimethylacetamide (Stewart & Siddall, 1970; Siddall, Stewart & Knight, 1970) and *N*-methylacetamide (Drakenberg & Forsén, 1971). For the latter compound the value of 18·8 kcal mole^{-1} refers to the *cis* → *trans* isomerization, the reverse process being 2·5 kcal mole^{-1} more costly.

Although the off-diagonal terms in Table 7 are small compared with the diagonal ones, they are by no means negligible in some cases. In principle, these terms can tell us how interactions between the four substituents affect the potential surface, but it is hard to see any systematic pattern.

Approach to an energy surface describing out-of-plane deformations of the amide group

From the discussion of the previous section it has been established that the force constant for out-of-plane bending at the carbonyl end of the amide group is much larger than those for twisting and out-of-plane bending at nitrogen (Table 7). In agreement with this, the structural data (Table 6) show that the amplitude of the χ_C deformation in non-planar amides is much smaller than the amplitudes of τ' and χ_N and can be neglected in an approximate description.

Although the equilibrium structure of the amide group is often assumed to be strictly planar, there are reasons for believing that the χ_N potential is rather flat around $\chi_N=0$. A planar amide group certainly ensures optimal bonding interaction between *p*-orbitals at trigonally hybridized carbon and nitrogen atoms, but this can only be achieved at the cost of the energy required to bring the three bonds at nitrogen into a common plane, an amount that can be identified with the inversion barrier of 5–6 kcal mole^{-1} in amines [Coon, Naugle & McKenzie (1966) (NH_3); Tsuboi (1967) (CH_3NH_2); Wollrab (1968) (CH_3NHCH_3)]. A slight pyramidalization at the nitrogen atom can thus be said to correspond to worse π-orbital overlap but to better hybridization. It is difficult to foresee exactly how these two opposing effects will balance out, but since they are of roughly similar magnitude (Dewar, 1969) the net effect should produce a very flat potential along the χ_N coordinate or even a double minimum with a small barrier at $\chi_N=0$. The experimental evidence that could distinguish between these two possibilities seems to be somewhat equivocal. From a microwave analysis of formamide, Costain & Dowling (1960) concluded that the equilibrium structure of this molecule is non-planar, with $\tau=2{\cdot}5°$, $\chi_N=19°$, $\chi_C=0°$; the energy barrier for inversion of the slightly pyramidal nitrogen atom was estimated to be 1·1 kcal mole^{-1}. Low frequency bands in the infrared spectrum of formamide in the gas phase and of acetamide in an argon matrix have been observed and attributed to the inversion vibration (King, 1971, 1972). However, the recent redetermination of the formamide structure by analysis of the microwave spectra of additional isotopic species gives a planar equilibrium structure with an extremely flat single minimum quartic potential function for the inversion (Hirota *et al.*, 1974). As far as quantum mechanical calculations are concerned, the CNDO/2 method leads to a distinctly pyramidal nitrogen ($\chi_N=25°$) in *N*-methylacetamide (Ramachandran, Lakshminarayan & Koleskar, 1973). However, the calculated inversion barrier is only about 0·3 kcal mole^{-1}.

Whether the planar structure corresponds to an energy minimum or to a slight energy maximum along the χ_N coordinate, it is clear that the behaviour of the potential function close to the planar structure cannot be harmonic. However, an increase in the double-bond character of the C′–N bond (as would occur in condensed phases, because of hydrogen bonding to the amide oxygen) should increase the resistance to out-of-plane bending at nitrogen. A harmonic potential, as assumed in many vibrational analyses and conforma-

tional calculations, may therefore be more justifiable if used in connection with experimental data from condensed phases. Another point to be considered is that twisting round the C'–N bond leads to diminished overlap between the π-orbitals and should therefore facilitate ouf-of-plane bending at nitrogen.

The τ', χ_N energy surface

The simplest expressions for the τ', χ_N energy surface that allow for the kind of behaviour mentioned above contain four potential constants. Out of the many possible functional forms, we have chosen one which has its energy minimum at the planar structure and which reduces to a harmonic potential along the line $\tau'=0$. It is thus more suited to describe the τ', χ_N energy surface for amides in condensed phases and has the following form:

$$V(\tau',\chi_N)=\frac{V_0}{2}(1-\cos\tau')+p_N\chi_N^2 + q_N(1-\cos\tau')[\exp(-\alpha\chi_N^2)-1]. \quad (9)$$

The values of the four constants V_0, p_N, q_N and α can be estimated by fitting the potential to the following facts and assumptions.

(*a*) V (180°, χ_N) has a minimum at $\chi_N=60°$ (pyramidal $\rangle$N– grouping with tetrahedral bond angles as in an amine).

(*b*) V (180°, 0)–V (180°, 60°)=6 kcal mole^{-1}, corresponding to the inversion barrier of ammonia.

(*c*) The energy barrier to *cis–trans* isomerization is 20 kcal mole^{-1}.

(*d*) The quadratic potential constant p_N is set at 6 kcal mole^{-1} rad^{-2}, a rough estimate based on the various vibrational analyses of amides (Table 7).

With all energy quantities in kcal mole^{-1} and angles in degrees we obtain $V_0=26{\cdot}0$, $p_N=1{\cdot}83\times10^{-3}$, $q_N=9{\cdot}075$, $\alpha=3{\cdot}28\times10^{-4}$. A plot of the function is shown in Fig. 7. With one exception the values of τ' and χ_N observed in non-planar amides (Table 6) correspond to energies that lie within 1·0 kcal mole^{-1} of that of the planar amide group. The exception is caprylolactam with V (34°, 23°)=2·9 kcal mole^{-1}, an amount which is comparable with the *cis–trans* energy difference of open-chain secondary amides. The occurrence of unstrained *cis* and strained *transoid* forms of this molecule in approximately equal amounts in solution equilibria is not surprising. The caprylolactam point is somewhat displaced from the minimum of the energy profile along the line $\tau'+\chi_N=$constant, but the energy difference with respect to this minimum is only 0·1 kcal mole^{-1}.

Our model is certainly still oversimplified. One obvious shortcoming is that it shows mirror symmetry across the lines $\tau'=0$, $\tau'=180°$ and $\chi_N=0$, whereas the deformations corresponding to points in the (+, +) and (+, −) quadrants are not structurally equivalent. One combination leads ultimately to eclipsing of the nitrogen lone pair with the C=O bond, the other to eclipsing with C'–C_α. However, the CNDO/2 calculations for *N*-methylacetamide (Ramachandran, Lakshminarayanan & Koleskar, 1973) gave an energy minimum close to $\omega_1\sim-167{\cdot}5°$, $\chi_N\sim-25°$, corresponding to $\tau'\sim0$, which suggests that asymmetric perturbation from the carbonyl end of the amide group is not too serious, at least for small τ'. Another shortcoming is that the simple potential (9) has periodicity 2π along τ' and hence does not distinguish between *cis* and *trans* amides. For a more complete description additional terms would have to be included to take care of interactions between substituents. These terms will depend on the detailed structure of the substituents and will vary from one amide to another and also with the local environment of the amide group.

The validity of equation (9) could be checked by suitable quantum mechanical calculations. The parametrization can undoubtedly be improved but we believe that its general form expresses essential features of that part of the potential energy surface for the τ', χ_N deformations which is characteristic of the hydrogen-bonded amide group.

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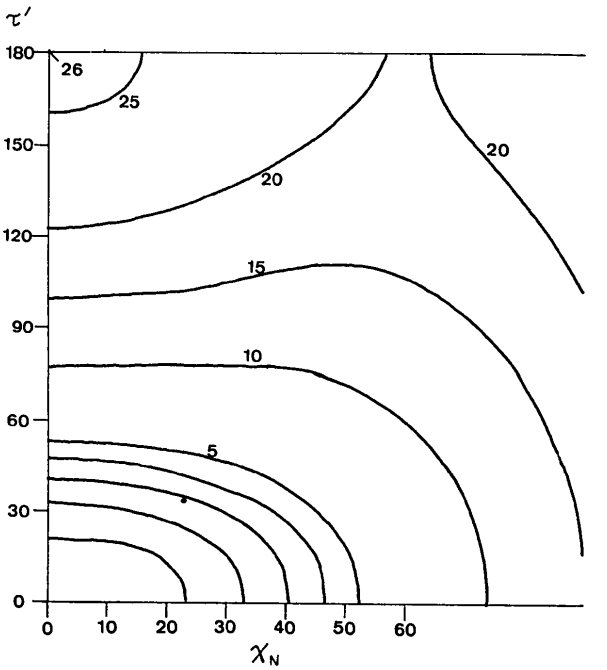

Fig. 7. Approximate form of $V(\tau',\chi_N)$ energy surface for amides in condensed phases.

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