Hydrogen bonds and geometry of amide groups in 2-[2-acyl-(2-isoquinolinyl)]cycloalkan-1,3-diones

E. V. Borisov,[a]* *Yu. G. Chernov,*[a] *L. G. Kuz'mina,*[b] *V. A. Tereshko,*[a] *and A. A. Akhrem*[a]

[a]*Institute of Bioorganic Chemistry, Academy of Sciences of Belarus',*
220141 Minsk, Belarus'
[b]*N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences,*
31 Leninsky prosp., 117907 Moscow, Russian Federation.
Fax: +7 (095) 954 1279

The geometry of the amide groups and hydrogen bonds (formed by the enol protons and amide oxygen atoms) in 2-[2-acyl-(2-isoquinolinyl)]cycloalkan-1,3-diones has been studied by X-ray diffraction analysis. The correlation between the C=O and N—C(O) distances, the parameters characterizing the nonplanarity of these groups, and the relative directions of the hydrogen bonds have been found.

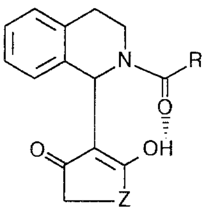
Key words: amide group; H-bond; isoquinoline derivatives, cycloalkandione derivatives, enols, structure; X-ray structural analysis.

The features of the structures of amide groups and the study of the effect of structural factors on their geometry are of considerable interest in view of the role that these groups play in protein molecules. Having studied the spatial structures of a considerable number of compounds, Pauling and Corey suggested as early as 1953 the concept of planarity of these groups based on the resonance principle.[1] More recently, compounds containing amide groups, the geometry of which substantially deviates from planarity, have been found.[2—8] This is generally true when the amide N atom or the amide bond are involved in small and moderate-size cycles. The largest deviations from planarity were observed in the cases when the N atom was involved in a three-membered cycle.[9] A series of moderate-size cycles containing amide bonds have been studied in detail.[10]

At present, it is established that the distortion of geometry may be caused not only by structural features of cycles, but also by intramolecular nonbonding, as well as intermolecular, interactions.[10,11] In particular, it has been demonstrated by X-ray diffraction method[10] that protonation of the amide group results in a decrease in the N—C(O) distance, an increase in the C=O distance, and a decrease in the N—C—O angle. However, the authors of this work[10] failed to find a rigorous relationship between the degree of flattening of the amide group and the degree of protonation. The effect of the angle of rotation about the amide group on the N—C(X) distance has also been studied.[11] The stability of planar acetamide in relation to the coordination of a water molecule has been investigated by computational methods.[12]

However, no data on the effect of the hydrogen bond with the carbonyl O atom on the geometry of the amide group have been reported. There are also no data on the possible correlation between the C=O and N—C(O) distances.

We have studied the spatial structures of a series of 2-[2-acyl-(2-isoquinolinyl)]cycloalkan-1,3-diones in a nonpolar solvent by the NMR technique[13] and we have established that the enol proton in these molecules forms a very strong intramolecular hydrogen bond with the carbonyl O atom of the amide group to afford an eight-membered chelate pseudocycle. In this work, we report the results of an X-ray diffraction study of certain of the molecules of the above-mentioned series (**1a—d**). These results deal with the structural features of their amide groups and the hydrogen bonds in which these amide groups are involved.



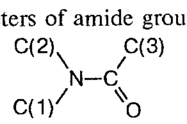
1a—d

a: R = Me, Z = CH_2CH_2
b: R = CH_2Me, Z = CH_2CMe_2
c: R = CH_2Cl, Z = CH_2CMe_2
d: R = Me, Z = CH_2

The principal geometric parameters for the amide groups and hydrogen bonds in the compounds studied are given in Table 1. The analysis of these parameters demonstrates that in compounds **1a,b,d** the intramolecular hydrogen bond is retained in the crystal, whereas in the case of **1c**, this bond is replaced with an intermolecular hydrogen bond, in which the enol proton is bonded to the carbonyl O atom of the amide group of the neighboring molecule. This is reflected mainly in the

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 107—109, January, 1995.

Table 1. Geometric parameters of amide groups and hydrogen bonds in compounds **1a—d**



Parameter	1a	1b	1c	1d
N—C^a	1.345(5)	1.333(4)	1.340(2)	1.339(5)
C=O^a	1.230(6)	1.252(4)	1.233(2)	1.241(4)
N—C=O^b	121.1(1)	121.1(3)	121.5(2)	121.4(3)
C(1)—N—C^b	118.2(4)	118.8(3)	117.2(1)	119.1(3)
$h_N{}^c$	0.072(4)	0.051(3)	−0.009(1)	0.008(3)
$h_C{}^c$	−0.007(4)	0.003(3)	−0.001(1)	−0.003(3)
C(1)—N—C=O^d	−9.4	−6.5	0.0	−3.5
C(1)—N—C—C(3)^d	171.7	173.1	179.1	176.8
C(2)—N—C=O^d	−178.9	−179.1	180.0	175.2
C(2)—N—C—C(3)^d	2.1	0.0	0.0	−4.5
N—C=O···H^d	13.6	26.8	12.9	36.2
l^e	0.344(3)	0.54(5)	−0.66(2)	0.79(5)
O—H^a	1.112(4)	1.14(5)	0.83(3)	1.09(5)
O···H^a	1.578(4)	1.43(5)	1.84(3)	1.52(5)
O—H···O^b	148.3	176.4	169.4	162.9
C=O···H^b	116.0(3)	124(2)	163.3(8)	119(2)
O···O^a	2.592(4)	2.565(3)	2.664(2)	2.578(4)

^{a} Distance (Å). ^{b} Planar angle (deg). ^{c} h_X(Å) is the pyramidality of the X atom, *i.e.*, the distance from the X atom to the plane formed by three atoms bonded to the X atom. ^{d} Dihedral angle (deg). ^{e} Distance (Å) from the bridging proton to the NCO plane.

O···H, O—H, and O···O distances and the C=O···H angle (see Table 1). The amide group in compound **1c** has essentially planar geometry (the dihedral angles are close to 0 or 180°, the value of h_N is quite insignificant, and h_C is equal to zero within the limits of the experimental error of the measurements), whereas in compounds **1a**,**b**,**d**, on the other hand, substantial deviations from planarity are observed (the dihedral angles characterizing the rotation about the amide bond for all three compounds are different from zero or 180° and from each other; h_N for two of these compounds have substantial values and are essentially different from each other). However, there are parameters (the N—C=O angle and the pyramidality h_C, which is close to zero) that are identical or very close for all four compounds within the limits of the error of the measurements (see Ref. 10).

Certain of the parameters (dihedral angles, the h_N value, the N—C=O···H angle, the l distance, and the C=O and N—C(O) bond lengths) have unique values for each compound. For compounds with a nonplanar amide group, a definite correlation between the changes in these values is observed. Thus, a decrease in the magnitude of the C(1)—N—C=O dihedral angle in the series of compounds **1a**,**b**,**d** is accompanied by an increase in the C(1)—N—C—C(3) and C(2)—N—C=O angles and a change in the C(2)—N—C—C(3) angle. These correlated changes reflect, on the one hand, the rotation of the two planes formed by the C(1)NC(2) and OCC(3) atoms relative to each other about the N—C(O) bond. On the other hand, the change in the sign of the C(2)—N—C—C(3) angle points to the appearance and increase in the degree of pyramidality of the N atom. The above-mentioned rotation is accompanied by increase in the degree of pyramidality of the N atom with the retention of the planar character of the C atom. The N—C=O···H angle and the l distance decrease as the degree of pyramidality and the tilting of the terminal groups of the amide group about the N—C(O) bond increases. The above-mentioned angle and distance characterize the location of the segment of the additional O···H hydrogen bond with respect to the plane through the NCO atoms: the smaller these values, the closer the position of this segment to the plane. Apparently, this relationship is attributable to the enhancement of the steric interaction of the carbonyl O atom with the atoms of the cyclic enolized β-diketone group and, primarily, with the oxygen atom of the OH group. Steric interactions of this type decrease the internal rotation barrier about the N—C(O) bond in *N*-ethyl-*N*-metylamides.[14] This also may be responsible for the fact that the attempts to find a clearly defined correlation between the flattening of the amide group and the degree of protonation of this group have not been successful.[10]

It should be noted that the C=O···H angle in the compounds with intramolecular hydrogen bonds is close to the statistical average value for hydrogen bonds in carboxylates, in which the steric hindrances are minimum.[15]

A correlation also exists between an increase in the nonplanarity of the amide groups in the series of compounds **1c**, **1d**, **1b**, and **1a** and chemical shifts of the enol proton in the ^{1}H NMR spectra (in $CDCl_3$) of the compounds under consideration (δ 11.50, 11.96, 12.34, and 12.36, respectively[1]).

A statistical analysis of changes in the C=O and N—C(O) distances in the series of compounds with intramolecular hydrogen bonds demonstrated that they are related to each other linearly:

$$d(\text{N—C(O)}) = a + bd(\text{C=O}),$$

where $a = 2.0$, $b = -0.55$, and the correlation factor is −1.0000. We analyzed the data on 51 pairs of distances taken from the Cambridge Structural Database[16] for compounds containing tertiary amide groups involved in different cycles, in which there are neither hydrogen bonds nor the conjugation of amide groups; using the same coordinates this analysis gave a very low correlation factor of −0.689, and $a = 2.9$, $b = -1.2$. The analysis of the data on the moderate-size cycles reported in the Ref. 10, which deals with the effect of protonation on the geometry of amide groups, showed, on the contrary, a very high correlation factor (−0.943) and a and b values (2.0±0.1 and −0.52±0.07, respectively) that agree within the limits of experimental error with the values determined by us (Fig. 1). This result is indicative of the fact that, although in the general case no rigorous

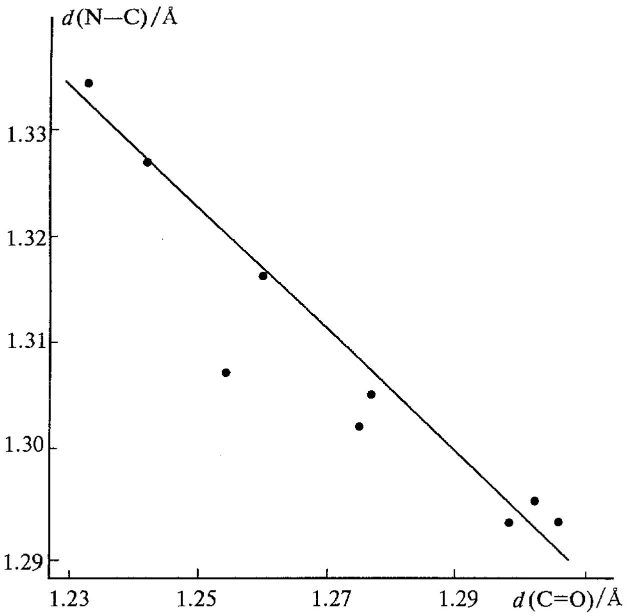


Fig. 1. Correlation between the N—C(O) and C=O distances. The experimental data were taken from the literature.[10]

relationship between the C=O and N—C(O) distances is found, when a hydrogen bond with the carbonyl O atom exists in the absence of other factors causing distortion of the geometry of the amide group, a linear relationship between *d*(C=O) and *d*(N—C(O)) is observed with constant values of *a* and *b*.

We also analyzed the relationship of *d*(C=O) and *d*(N—C(O)) to the O· · ·O distance. It turns out that in this case, the correlation factor within the limits of the linear model also has a high value. In the case when the O· · ·O distance is an independent variable, the *a* and *b* parameters for the C=O and N—C(O) distances (dependent variables) are equal to 0.44±0.01, −0.81±0.02 and 0.19±0.03, 3.3±0.0, respectively, and the correlation factors are −1.000 and 1.000 (here and above, the standard deviations were not corrected for the limited number of experimental points). Unfortunately, because of the lack of complete experimental data, this result cannot be taken as the net result.

Experimental

X-ray structural analysis of crystals was performed at room temperature on Nicolet R3m (compound **1a**), Enraf-Nonius (compounds **1b**,**d**), and Syntex P21 (compound **1c**) diffractometers (Mo-Kα radiation, graphite monochromators, empirical absorption corrections were applied). For compound **1b**, the space group is $P2_1/a$; for the remaining compounds, the space group is $P2_1/n$. The unit-cell parameters for crystals of **1a**,**b**,**c**,**d** are as follows: a = 12.979(3), 10.681(1), 11.422(3), and 12.105(2) Å, respectively; b = 9.276(4), 11.161(1), 11.441(4), and 9.371(2) Å, respectively; c = 13.438(4), 14.879(2), 14.652(4), and 13.353(1) Å, respectively; β = 116.13(2)°, 96.28(1)°, 111.64(2)°, and 115.10(1)° and $2\theta_{max}$ = 54°, 50°, 62°, and 54°, respectively.

All of the structures were solved by the direct method and were first refined isotropically by the least-squares method and then anisotropically (for nonhydrogen atoms) by the full-matrix least-squares method. Initial coordinates for all of the hydrogen atoms of compound **1c** were obtained from the difference Fourier synthesis; B_{iso} were taken as 6 Å^2. For the remaining compounds, coordinates for only the bridging atom were obtained by this method. Coordinates were refined using the riding model. However, for compound **1a** within the limits of this model, the contributions of all H atoms were taken into account, whereas for compounds **1a** and **1d**, the bridging atom was fully independent and refined isotropically. The final *R* factors for compounds **1a**,**b**,**c**,**d** were 0.061, 0.032, 0.042, and 0.038, respectively.

All calculations were carried out on an IBM PC/AT personal computer using the SHELX-86 and SHELX-76 program packages.

References

1. R. B. Corey and L. Pauling, *Proc. Roy. Soc. London, Ser. B,* 1953, **B141,** 10.
2. R. P. Shibaeva, L. O. Atovmyan, and R. G. Kostyanovsky, *Dokl. Akad. Nauk SSSR,* 1967, **175,** 586 [*Dokl. Chem.,* 1967, **175** (Engl. Transl.)].
3. L. V. Vilkov, I. I. Nazarenko, and R. G. Kostyanovsky, *Zh. Strukt. Khim.,* 1968, **9,** 1075 [*J. Struct. Chem.,* 1968, **9** (Engl. Transl.)].
4. F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.,* 1971, **59,** 169.
5. L. L. Reed and P. L. Johnson, *J. Am. Chem. Soc.,* 1973, **95,** 7523.
6. J. A. Lerbscher and J. Trotter, *J. Cryst. and Mol. Struct.,* 1972, **2,** 67.
7. V. Amirthalingam and V. S. Jakkal, *Acta Crystallogr.,* 1972, **B28,** 2612.
8. T. Matsuzaki and Y. Iitaka, *Acta Crystallogr.,* 1971, **B27,** 507.
9. G. V. Shustov, G. K. Kadorkina, S. V. Varlamov, A. V. Kachanov, R. G. Kostyanovsky, and A. Rauk, *J. Am. Chem. Soc.,* 1992, **114,** 1616.
10. J. D. Dunitz and F. K. Winkler, *Acta Crystallogr.,* 1975, **B31,** 251, 264, 268, 270, 273, 276, 278, 281, 283, 286.
11. G. Gilli and V. Bertolasi, *J. Am. Chem. Soc.,* 1979, **101,** 7704.
12. N. G. Mirkin and S. Krimm, *J. Am. Chem. Soc.,* 1990, **112,** 9016.
13. A. A. Akhrem, E. V. Borisov, and Yu. G. Chernov, *Zh. Org. Khim.,* 1990, **26,** 1114 [*J. Org. Chem. USSR,* 1990, **26** (Engl. Transl.)].
14. H. G. Bonacorso, M. S. B. Caro, N. Zanatta, and M. A. P. Martins, *MRC,* 1993, **31,** 451.
15. C. H. Gorbitz, M. C. Etter, *J. Am. Chem. Soc.,* 1992, **114,** 627.
16. *Cambridge Structural Database,* University Chemical Laboratory, Cambridge (England), 1988.

Received November 29, 1993;
in revised form July 19, 1994