Research Article

Journal of Physical Organic Chemistry

Received: 30 January 2008, Revised: 10 April 2008, Accepted: 13 April 2008, Published online in Wiley InterScience: 2 June 2008

(www.interscience.wiley.com) DOI 10.1002/poc.1390

Does the five-member hydrogen bond ring in quinoline carboxamides exist?

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The presence of intramolecular NHN hydrogen bond in 4-*R*-quinoline-2-(*N*-*R*′-carboxamides) was investigated by AIM methodology. Values of electron density, elipticity, and total energy density at the bond critical point of H···N in amides were compared with respective values of H···O in their *N*-oxides. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: amides; intramolecular hydrogen bond; electron density; AIM calculations

INTRODUCTION

Very special role of intramolecular hydrogen bond in determination of the conformation of compounds and their chemical, physical, and biological properties is well known.[1–3] The energy of hydrogen bonds varies from about 100 kJ/mol for interactions of partially covalent character to very weak interactions of about 1 kJ/mol. It is not easy to differentiate the very weak hydrogen bond and non-specific interaction.[4] In the literature one can find various criteria of hydrogen bonds: geometrical, energetic, spectroscopic, or functional.[2,4] Each of them is accurate and useful for particular interaction, but at the same time it does not have a general character. For weak interactions, conclusions concerning the presence or lack of the hydrogen bond based on different criteria have been sometimes contradictory.[5–8] The weak intramolecular hydrogen bonds NH···O and NH···N in amides, polypeptides, and proteins have been objects of numerous studies because of their biological importance.[7,9–20]

The aim of this work is to answer the question concerning formation of the intramolecular NH···N hydrogen bond in the five member ring in 4-*R*-quinoline-2-(*N*-*R*′-carboxamides). Existence of the intramolecular NH···N hydrogen bonds in quinolinecarboxamides has been in question.[15–20]

One of the theoretical methods that have been recently shown to be useful in detection and studying the intramolecular hydrogen bonds is the method based on AIM theory of Bader.[5,7,12,21–25] In frame of the AIM theory, Poplier has proposed criteria of the presence of the hydrogen bond[21] as follows:

- On the bond path, H···B linking the H and B atoms of the bond critical point (BCP) must be present.
- The value of the charge densities at BCP of the hydrogen bond H···B ($\rho_{H\cdots B}$) should be within the range of 0.002–0.040 a.u. Recently Alcorta *et al*. suggested that the lowest the $\rho_{H\cdots B}$ values is to be greater than 0.01 a.u.[27]
- Laplacian ($\nabla^2_{H\cdots B}$) of electron density at the BCP should be within 0.024–0.139 a.u. range.

Except the criteria listed above, the value of the total energy density of the electron at BCP ($H_{H\cdots B}$) has been shown to characterize the relative hydrogen bond strength.[22,26–28] The $H_{H\cdots B}$ is the sum of potential ($V_{H\cdots B}$), energy density that is related to the action which builds up the hydrogen bond interactions accumulating the electrons around the BCP, and kinetic energy density ($G_{H\cdots B}$) related to the mobility of the electrons. The negative value of $H_{H\cdots B}$ indicates the partly covalent character of the hydrogen bond.

In this work, we have applied the AIM analysis to search out the intramolecular hydrogen bond in five-member chelate ring of *4-R-quinoline-2-(N-R′-carboxamides)*. For comparison we have used this same method for their *N*-oxides, where the presence of the intramolecular NH···O hydrogen bond in the six-member ring has been evidenced by spectroscopic method.[29,30]

COMPUTATIONAL DETAILS

To decide which optimization method is the best to reproduce the structure of the investigated compounds the molecule of *quinoline-2-carboxamide* was optimized at HF/6-311++G**, B3LYP/6-311++G**, and MP2/6-311++G** level and the geometric parameters of the NHN bridge were compared. The obtained N···N (H···N) distances were 2.691 (2.308), 2.690 (2.271), and 2.679 (2.249) Å and the NCC (NHN) angles were 115.15 (101.76), 114.32 (103.46), and 113.97 (104.06)°, respectively. The results for B3LYP/6-311++G** method was discussed in following, although it was checked that every method reproduces the correlations presented in the paper. The investigated compounds were optimized at the DFT B3LYP/6-311++G** level of calculation using the Gaussian 03 program.[31] To verify that the absolute minimum on the potential energy surface was reached, all vibrational frequencies were checked to be positive. The wave function evaluated for each optimized structure was used as the input to the AIM2000 program.[32]

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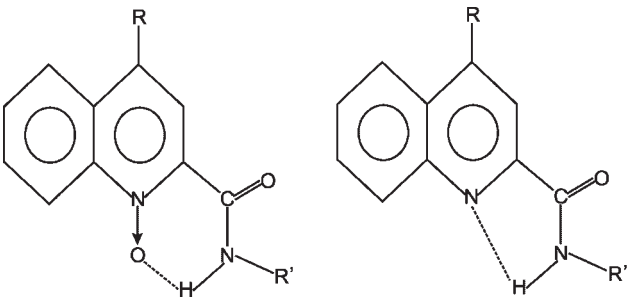
RESULTS AND DISCUSSION

The intramolecular hydrogen bond in six-member ring is very common and stabilizes the conformation of the compound. For five-member rings it is just the conformation which facilitates the formation of intramolecular hydrogen bond. However, due to the strain reasons and nonlinearity of the hydrogen bridge, this hydrogen bond is very weak. For this reason, existence of the five-member ring is sometimes questioned.

In this work we have applied the AIM analysis for comparing the interaction between the amide NH group and *N*-oxide groups in the six-member chelate ring in *4-R-quinoline-2-(N-R′-carboxamide)-N-oxides* (Scheme 1), where existence of the intramolecular hydrogen bond (NH···O) is well confirmed[29,30] with those between the NH group and the heterocyclic N-atom (NH···N) in *4-R-quinoline-2-(N-R′-carboxamides)*. As it has been mentioned in the 'Introduction' section, the main objective of our work is to answer the question concerning the formation of the intramolecular NH···N hydrogen bond in the five-member ring in 4-*R*-quinoline-2-carboxamides.



Scheme 1.

4-R-quinoline-2-(N-R′-carboxamide) N-oxides

The calculated topological properties of the electron density at the BCP participating in the NH···O hydrogen bonds in series of *4-R-quinoline-2-(N-R′-carboxamide) N-oxides* with the different substituents in the position 4 on the quinoline ring (R = H, Me, OEt) and linked to the *N*-amide atom (R' = H, Me, *t*-Bu, Ph) (Scheme 1) have been collected in Table 1. The calculated value of $\rho_{H\cdots O}$ ranges from 0.037 to 0.049 a.u. The respective values of $\nabla^2_{H\cdots O}$ are in the range from −0.134 to −0.153 and the $H_{H\cdots O}$ values are from −0.031 to −0.837 range. All these values are in accordance with the presence of the medium strength hydrogen bond.[28] The inspection of the Table 1 shows that the values of the electron densities at BCP of H···O bond increase with electron donor properties of the *R*-substituent in the quinoline ring are in order of: OEt > Me > H that is in accordance with the increase of the oxygen atom basicity. For particular *R*-substituent, the electron densities of $\rho_{H\cdots O}$ increases with the substituent R' linked to the amide N atom in order: Ph > *t*-Bu > Me > H. This indicates the strengthening of the hydrogen bond accordingly to the expected substituent effect on the acidity of the NH group. The negative values of $H_{H\cdots O}$ indicate the partially covalent character of the H···O bond.[12,28] Espinosa *et al*.[27] proposed to use the $|H_{H\cdots B}|/(\rho_{H\cdots B})$ ratio as a measure of the covalency of the bond.[26] For amides under study, this parameter increased with the hydrogen bond strength from −0.832 to −17.178, proportionally to the values of $\rho_{H\cdots O}$ for given *R*-subsituent. For intramolecular hydrogen bond, when the six-member ring is formed, the ring critical point (RCP) has been shown to be a good descriptor of the hydrogen bond.[23,24] For the series of *N*-oxide amides, the topological parameter for the RCP (ρ_{RCP}) in the chelate ring with hydrogen bond has been calculated (Table 2). The ρ_{RCP} values increase linearly with the $\rho_{H\cdots O}$ (Fig. 1). Similar correlation was found by Grabowski *et al*.[24,25]

4-R-quinoline-2-(N-R′-carboxamides)

Topological parameters of H···N and NH bonds of *4-R-quinoline-2-(N-R′-carboxamides)* (R = H, Me, OEt; R' = H, Me, *t*-Bu, Ph) (Scheme 1) have been presented in Table 2. Based on the spectroscopic criteria in *quinoline-2-carboxamide* (***R*** = ***R′*** = **H**), the hydrogen bond was not found.[15,16] For secondary *quinoline-2-(N-methylcarboxamide)* (**R = H, R′ = Me),** X-ray analysis showed a distinct nonlinearity of the NHN bond (NHN = 96°) that might eliminate the possibility of the hydrogen bond formation,[18] however, IR spectroscopic studies suggested the existence of the NH···N bond.[19,20] The presence of the intramolecular hydrogen bond has also been suggested for *quinoline-2-(N-t-butylcarboxamide)*.[20] In situation when the

Table 1. Bond and ring critical points for hydrogen bond in 4-*R*-quinoline-2-(*N*-*R′*-carboxyamide) *N*-oxides [a.u.]

		H···O				NH				
R	*R′*	$\rho_{H\cdots O}$	$\nabla^2\rho_{H\cdots O}$	$H_{H\cdots O}$	$\varepsilon_{H\cdots O}$	ρ_{NH}	H_{NH}	ε_{NH}	ρ_{RCP}	Δ [Å]
H	H	0.037	0.134	−0.031	0.031	0.330	−77.712	0.045	0.015	1.197
H	Me	0.039	0.139	−0.175	0.048	0.330	−77.398	0.047	0.016	0.645
H	*t*-Bu	0.041	0.142	−0.300	0.053	0.329	−76.505	0.046	0.016	0.641
H	Ph	0.045	0.149	−0.603	0.051	0.326	−76.549	0.041	0.017	0.656
Me	H	0.037	0.136	−0.075	0.031	0.330	−77.555	0.044	0.022	2.806
Me	Me	0.040	0.140	−0.207	0.047	0.330	−77.241	0.046	0.016	0.649
Me	*t*-Bu	0.042	0.143	−0.350	0.054	0.328	−76.244	0.046	0.016	0.598
Me	Ph	0.046	0.150	−0.655	0.052	0.325	−76.330	0.041	0.016	0.660
OEt	H	0.040	0.140	−0.195	0.040	0.326	−77.021	0.043	0.016	0.667
OEt	Me	0.042	0.143	−0.326	0.050	0.327	−76.765	0.046	0.016	1.837
OEt	*t*-Bu	0.042	0.140	−0.375	0.054	0.328	−76.228	0.046	0.016	0.647
OEt	Ph	0.049	0.153	−0.836	0.054	0.322	−75.534	0.040	0.017	0.672

Table 2. Bond and ring critical points for hydrogen bond in 4-R_1-quinoline-2-(*N*-R_2-carboxyamides) [a.u.]

		H···N				NH				
R	*R′*	$\rho_{H\cdots N}$	$\nabla^2\rho_{H\cdots N}$	$H_{H\cdots N}$	$\varepsilon_{H\cdots N}$	ρ_{NH}	H_{NH}	ε_{NH}	ρ_{RCP}	Δ [Å]
H	H	0.017	0.078	0.017	1.175	0.051	−76.782	0.051	0.017	0.034
H	Me	0.019	0.081	0.018	0.522	0.051	−76.220	0.051	0.018	0.079
H	*t*-Bu	0.020	0.083	0.019	0.450	0.053	−75.604	0.053	0.019	0.090
H	Ph	0.022	0.089	0.020	0.311	0.047	−76.595	0.047	0.020	0.128
Me	H	0.018	0.078	0.017	1.132	0.051	−76.763	0.051	0.017	0.036
Me	Me	0.019	0.081	0.019	0.492	0.051	−76.204	0.051	0.019	0.083
Me	*t*-Bu	0.020	0.083	0.019	0.434	0.053	−75.612	0.053	0.019	0.092
Me	Ph	0.022	0.090	0.020	0.301	0.047	−76.573	0.047	0.020	0.131
OEt	H	0.018	0.079	0.018	0.976	0.051	−76.836	0.051	0.018	0.042
OEt	Me	0.020	0.082	0.019	0.465	0.051	−76.239	0.051	0.019	0.087
Oet	*t*-Bu	0.021	0.085	0.019	0.433	0.053	−75.582	0.053	0.019	0.093
Oet	Ph	0.023	0.090	0.021	0.284	0.047	−76.558	0.047	0.021	0.135

Δ – distance between RCP and BCP.

experimental investigations give unequivocal results, the AIM analysis seems to be the proper method to answer the question on the existence of the intramolecular hydrogen bond. As it can be seen from the Table 2, the values of $\rho_{H\cdots N}$ are in the range of 0.017–0.023 and the values of $\nabla^2_{N\cdots O}$ are in 0.078–0.087 a.u. range. These values, however very low, are in accordance with the criteria of hydrogen bond existence.[21] Low values of the electron densities and positive values of the total energy density at BCPs suggest the weak interaction of purely electrostatic nature. The obtained values of $\rho_{H\cdots N}$ and $\nabla^2_{N\cdots O}$ are similar to the calculated topological parameters for intramolecular hydrogen bond in five-member chelate ring of *N-formyltriglycine amide*[7] and the C7 conformers of *N-acyl-L-alanine N′-methylamide*.[12] An argument for classification of the H···N interaction in *4-R-quinoline-2-(N-R′-carboxamides)* as hydrogen bond is also the correlation of the electron densities at $\rho_{H\cdots N}$ versus ρ_{NH} that fit this same equation as the $\rho_{O\cdots H}$ versus ρ_{NH} (Fig. 2). Also the linear dependence between the electron densities at the BCP in the N···H and O···H hydrogen bonds (Fig. 3) support classification of the H···N interactions as the hydrogen bond. In discussion of the

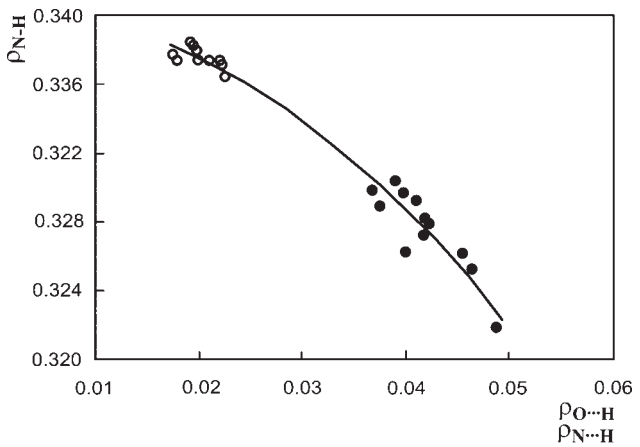


Figure 2. Correlation of the electron density at BCP of NH bond with the electron density at BCP of the H···O and H···N interaction ($y = -7.3242x^2 - 0.002x + 0.3405$, $R^2 = 0.9723$). Full points – $\rho_{H\cdots O}$, empty points – $\rho_{H\cdots N}$

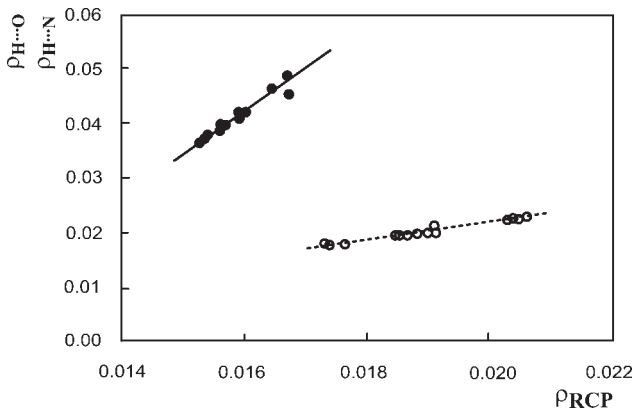


Figure 1. Correlation of the electron density at BCP of H···O and H···N interaction with the electron density at six-member and five-member ring critical point. Full points – $\rho_{H\cdots O}$, ($y = 7.3378x - 0.0753$, $R^2 = 0.9467$), empty points – $\rho_{H\cdots N}$ ($y = 1.5755x - 0.0098$, $R^2 = 0.9811$)

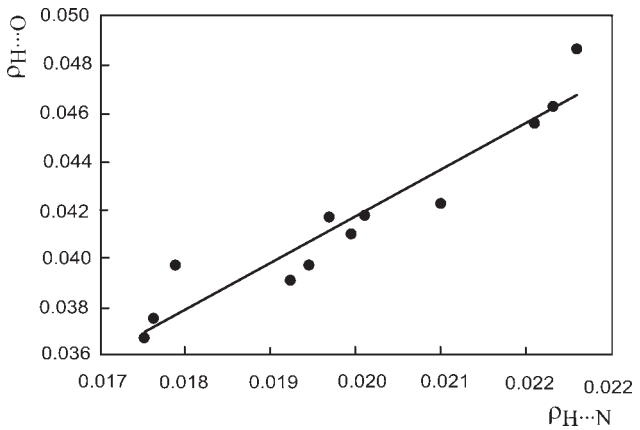


Figure 3. Correlation of the electron density at BCP of H···O bond with the electron density at BCP of the H···N interaction ($y = 1.927x + 0.0032$, $R^2 = 0.9064$)

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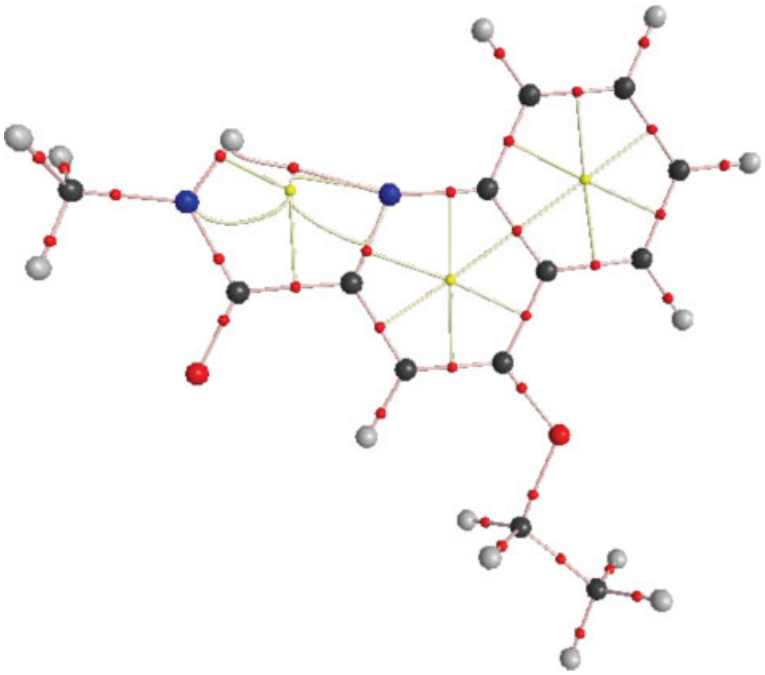

Figure 4. Molecular graph of 4-ethoxyquinoline-2-(*N*-methylcarboxamide)

hydrogen bond formation, except the values of the electron densities and energy density at BCP, the curvature of the bond path and the distance between the BCP and RCP must also be taken into account.[7,12,22] An example of molecular graph for *4-ethoxyquinoline-2-(N-methylcarboxamide)* is included to illustrate the five-member ring in amides (Fig. 4). The H···N bond paths in the studied amides are curved (Fig. 4) and the distances between the BCP and RCP are very small (Table 2). This indicates the great instability of the interaction and facility of the disruption of the N···H hydrogen bond by slight structural changes. The H···B interaction may also be described by the elipticity (ε_b) of the electron density at BCP; the large value of this parameter indicates the instability of the hydrogen bonding.[7,21,22] The elipticity values for H···N BCP in amides are ten times higher than the elipticity of O···H in *N*-oxides (Tables 1 and 2). These high values of ε_b for H···N hydrogen bond confirm the high instability of the hydrogen bond in amides. For quinoline-2-carboxyamide, the very small values of $\rho_{H\cdots N}$, exceptionally large values of elipticity and proximity of the RCP and BCP close to annihilation, indicate that the H···N interaction is on the verge of the hydrogen bond and non-specific interactions may be easily broken.[7,21,22] Stability of the conformation of the quinoline-2-carboxamides cannot be determined by the weak NH···N intramolecular hydrogen bond, but rather by a coupling of amide group with the aromatic ring.

CONCLUSIONS

Intramolecular hydrogen bond in *quinoline-2-carboxamides* and their *N*-oxides has been studied by AIM methodology. In *R-quinoline-(N-R′-carboxamide) N-oxides*, the intramolecular NH···O hydrogen bond of partly covalent character is present; influence of the substituent on the hydrogen bond strength has been discussed. For secondary *R-quinoline-(N-R′-carboxamides)* with the five-member chelate ring, the calculated topological properties of the electron densities in H···N hydrogen bond indicate the presence of very weak intramolecular hydrogen bond of the pure electrostatic nature. The primary *R-quinoline-N-carboxamides* fulfill the criteria of the existence of the hydrogen bond, however, the values of electron density are on the verge of formation of the H···N critical points. These results indicate that the stability of the conformation of the primary and secondary *quinoline-2-carboxamides* cannot be determined by the H···N interactions and it is the conformation of the amide group that facilitates the formation of the intramolecular hydrogen bond.

Acknowledgements

We thank the Wrocław Center for Networking and Supercomputing and for their generous computer time.

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