Electron density of a new EGFR Tyrokinase-inhibitor at 100K, consideration of different models.

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Abstract. The electron density (ED) of a substituted 4-(indol-3-yl)-quinazoline, a newly developed anti-cancer drug, was determined from a high resolution X-ray data set measured at 100K using synchrotron radiation. Because the structure contains a chlorine atom, which has a diffuse outer electron shell and is therefore beyond standard modeling, the influence of the model on the bond topological and atomic properties was studied following Bader's approach of 'Atoms In Molecules' (AIM). The expansion/contraction parameters κ and κ' of the four atoms being constitutive for the Cl-C-bond and the F-C-bond were obtained by calculation of theoretical structure factors of a model compound and assigned in subsequent multipole refinements. The κ and κ' -values for all other non H-atoms atoms were taken from the literature. The effect of two different sets of κ and κ' (1.20/1.20 and 1.13/1.29) for the hydrogen atoms was evaluated for the topological properties at bonds to hydrogen atoms (including hydrogen bonds) and to the atomic properties of the hydrogen atoms. Furthermore the effect of

particular n_1 -sets for the chlorine atom to bond topological descriptors of the Cl-C-bond was investigated for the theoretical structure factors and compared with experiment. All results were compared with corresponding theoretical findings from a single point calculation at experimental geometry.

Charge density / Anti-cancer drugs / Synchrotron experiments / Single crystal structure analysis / X-ray diffraction

1. Introduction

Conventional chemotherapy which is applied for elimination of cancer cells is little specific and has therefore the disadvantage of a significant amount of adverse effects, so that the development of more specific drugs is of particular interest. Since the progression of cells is controlled by growth factors, they are attractive targets for therapy. After being linked to an extra cellular receptor those factors initiate an intra cellular signal transduction, a chemical cascade, which leads in case of cancer to proliferation, angiogenesis, metastasis and invasion and a decreased ability for apoptosis. A lot of solid tumors over-express the epidermal growth factor receptor (a tyrosine-kinase, EGFR-TK) of which 40 to 100 are in a healthy body cell and up to two million in a malignant one, many of them as products of the cancer initializing oncogenes (fatal DNA-errors). This is often used as marker for an advanced case [1].

Inhibition of this signal transduction can be realized by blocking the extra-cellular receptor domain with antibodies or the intra-cellular tyrosine-kinase domain with small inhibitor molecules. Substituted 4-anilino-chinazolins (I) are known as potent EGFR-specific inhibitors of the tyrosine-kinase domain and are already in use in cancer therapy. A new approach deals with substituted 4-(indol-3-yl)-quinazolines (II) [1]. Both general structure types are given in Figure 1 together with a model compound, introduced in chapter 2.2.

Figure 1: Substituted 4-anilino-quinazoline (I) and 4-(indol-3-yl)-quinazoline (II). R1-R4: variable residues. Model compound 5-chloro-6-flouro-indol (III), see chapter 2.2.

For a rational drug design of optimized pharmaceutical active compounds not only steric but also electronic information is of fundamental relevance, since in biologically interacting systems, e.g. between a macromolecular target protein and a low-molecular substrate, chemical recognition is dominated by intermolecular interactions, which are caused by steric and electronic effects. Small structural variations like the interchange of single atoms, which may be potential donors or acceptors in hydrogen bonds, can lead to a modified behavior of the compound *in vivo*. High resolution X-ray diffraction at low temperatures and *ab initio* calculations at experimental geometry which have been performed in this study are proper tools for the quanti-

tative evaluation of the total electron density and related topological and atomic properties. The electrostatic potential gives further insight into the distribution of charge on the substrate molecule and, considering the key-lock arrangement, may enable a rough prediction of its orientation in the protein after ligation. Experimental electron density distributions also contain information on weak intermolecular interactions in the crystal. They can serve in a first approximation as a model for the interactions under biological conditions, since the same types of effects as the ligand-target interactions should exist in the crystal (e.g. steric, electrostatic, hydrogen bonding, van der Waals effects), and these are expected to be comparable in size.

Recently the regio-selective reactivity of another protease inhibitor was examined via a high resolution X-ray diffraction experiment [2]. The macromolecular structure of an EGFR kinase domain alone and complexed with an anilino-quinazoline-derivative was determined at a resolution of 2.6 Å [3] and the binding site of several EGFR inhibitors were studied by molecular field analysis and molecular docking studies [4]. No such study exists with an indole-quinazoline derivative, so that no information on the interaction of these types of substances with its host are available. Nevertheless, due to its expected pharmaceutical properties as improved anti-cancer drug an experimental and theoretical ED-study was carried on the title compound (IIa) where R1-R4 in Fig.1 are as follows: R1 = methoxyl, R2 = 4-(morpholin-4-yl)-propoxyl, R3 = chlorine, R4 = fluorine.

2. Experimental and Refinement Procedure

2.1 Measurement and data processing

The title compound (IIa) was synthesized and crystallized as previously described [1]. A single crystal with dimensions 0.45 x 0.2 x 0.2 cm was chosen for high-resolution X-ray diffraction data collection with synchrotron radiation at the beamline F1 of storage ring DORIS III at HASYLAB/DESY in Hamburg, which is equipped with a large Huber 4-circle diffractometer (in κ -geometry plus a second concentric detector-axis) and a MARCCD 165 area detector. The primary radiation was adjusted at a wavelength of 0.56 Å and the temperature at 100K using an open flow nitrogen gas stream. At detector 2 θ positions of 0° and 50° a total number of 960 frames were collected with a scan width of 3.0° in ϕ and an exposure time of 4 and 90 s, respectively (crystal to detector distance: 70.5 mm). 470578 reflections were measured up to a resolution of $\sin\theta/\lambda = 1.11 \text{ \AA}^{-1}$ ($d = 0.45 \text{ \AA}$) with an overall completeness of 99.9%.

The frames were integrated with the program XDS [5], scaling and merging was performed with the program SORTAV [6]. SHELXS-97 [7] was applied for the determination of the so far unknown structure, the refinement of the conventional spherical parameters was executed with SHELXL-97 [7] to obtain reasonable starting values for the

subsequent aspherical refinement. See Table 1 for more details.

CCDC-677806 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336033. Supplementary material for this paper contains integrated atomic properties (volumes and charges), the bond topological properties of the hydrogen bonds and static deformation density maps.

Table 1: Crystallographic data and experimental conditions for (IIa)

2.2 Multipole refinement of experimental and theoretical structure factors

The Hansen and Coppens multipole formalism [8], implemented in the program package XD [9], was applied for the aspherical atom treatment. In this approach the aspherical atomic density is described by

$$\rho_a(\vec{r}) = P_c \rho_c(r) + P_v \kappa^3 \rho_v(\kappa r) + \kappa'^3 \sum_{l=1}^4 R_l(\kappa' r) \sum_{m=1}^l P_{lm\pm} Y_{lm\pm}(\vec{r}/r) \quad (1)$$

The first two terms are spherically averaged core (ρ_c) and valence densities (ρ_v). $Y_{lm\pm}$ are spherical harmonic angular functions to describe the aspherical deformation density. The R_l are normalized Slater-type radial functions defined as

$$R_l(r) = \kappa'^3 \frac{\zeta^{n_l+3}}{(n_l+2)} (\kappa' r)^{n_l} \exp(-\kappa' \zeta r) \quad (2)$$

where r is the radial coordinate and ζ is the fixed single Slater energy optimized exponent [10]. The n_l can be given any positive integer numbers which observe $n_l \geq 1$.

In the multipole refinement the P_v and $P_{lm\pm}$ populations are refined. In addition the spherical and aspherical expansion/contraction parameters κ and κ' can be refined which might lead, especially for κ' , to correlation and hence to convergence problems. To account for this problem it was decided in the present study to obtain κ' values from the following approach:

For all non H atoms except for the four atoms involved in the C-halogen bonds (i.e. C(15), Cl(15), C(16), F(16), for atom numbering see Fig. 2), the κ and κ' values were taken from [11] and kept fixed. For the above mentioned four atoms the geometry optimized structure (B3LYP/6-311++G** [12]) of the smaller model compound 5-chloro-6-flouro-indole (III, see Fig. 1) was entered into TONTO [13] to calculate theoretical structure factors from the wavefunction file. From a subsequent multipole refinement of the theoretical structure factor data set κ and κ' values were obtained which were assigned to the four atoms in question. The resolution was limited to the experimental value in the theoretical refinement. The further refinement of experi-

mental data was carried out up to hexadecapolar level for the non H atoms while bond directed dipoles were used for the hydrogen atoms.

Two sets of κ, κ' values were examined for the hydrogens: (i) default values $\kappa = \kappa' = 1.20$ (hereafter called model *def*) and (ii) κ and κ' values of 1.13 and 1.29 introduced by Volkov [11], model *var*.

In order to account for chemical symmetry and to reduce the number of variables local site symmetries and constraints were imposed on the refinement of the experimental data. The densities of the atoms C(28) and C(29) were constrained to be identical to C(25) and C(26), respectively, because they were considered to be chemically equivalent. The same was applied for chemically equivalent hydrogen atoms. A local mirror symmetry was applied to all atoms of the planar quinazoline and indole fragments, to O(7) of the methoxyl residue, to the complete propoxyl fragment and to the four methylene carbon atoms in the morpholine part. C_{3v} symmetry was imposed on C(71) and cylindrical symmetry (only multipoles with $m_l = 0, l = 1 \dots 4$, were refined) on chlorine and fluorine.

The hydrogen-atom positions were set to distances given in the literature [14] from neutron diffraction experiments, because neutron data of this compound are not available.

Further attention was directed to the modeling of the bond to the chlorine atom, since the second row elements are known as border line cases for the modeling within the single-zeta approach in experimental electron density analysis [15], [16]. A detailed discussion will be made in chapter 4.

2.3 Theoretical calculations

For the evaluation of theoretical bond topological and atomic properties a single point *ab initio* calculation [12] of the title compound based on the experimental geometry at the B3LYP/6-311++G** level was carried out. The bond and atomic properties were obtained by the use of AIM2000 [17]. Theoretical deformation densities were obtained and displayed with the program MOLDEN [18].

3. Results and discussion

3.1 Molecular and crystal structure

The numbering scheme and displacement ellipsoids (ORTEP-plot [19]) of the title compound (IIa) at 100K is given in Figure 2. The positions 6 and 7 of the quinazoline fragment are substituted by a 4-(morpholin-4-yl)-propoxyl and a methoxyl residue, respectively. At the indole-fragment, the positions 5 and 6 are substituted by chlorine and fluorine, respectively.

Figure 2: ORTEP-plot [19] of the title compound (IIa). Probability at 50%.

It was originally speculated that the indole N-H might form an intramolecular hydrogen bond to the morpholine oxy-

gen. This was not found to be true. Instead (IIa) builds a dimer in the crystal, two molecules are connected via a center of symmetry through the intermolecular hydrogen bond N(11)–H(11)⋯O(27) with $d(\text{O} \cdots \text{N}) = 2.8052(9) \text{ \AA}$. Figure 3 displays a SCHAKAL-representation [20] of the dimer. A weak intramolecular hydrogen bond C(14)–H(14)⋯N(3) forming a distorted six-membered ring connecting both aromatic fragments exists, too. This is enabled by an almost coplanar arrangement of the quinazoline and the indole fragments, the interplanar angle is 28.8° . In the propoxyl chain linking the quinazoline aromate with the morpholine ring, a *trans* arrangement is found along C(21)–C(22) (torsion angle O(6)–C(21)–C(22)–C(23) = $167.0(3)^\circ$) while the torsion angle along N(24)–C(23)–C(22)–C(21) is close to 60° ($52.2(4)^\circ$) indicating a *gauche* arrangement at N(24) with respect to C(21). The morpholine 6-membered ring exhibits the expected chair form with C(23) as equatorial substituent.

Figure 3: SCHAKAL-representation [20] of the dimer formed via the strongest hydrogen bond of the title complex.

3.2 Charge density and topological analysis

The deviations between model *def* and *var* concerning the bond topology never exceed $0.05 \text{ e\AA}^{-3}$ in $\rho(\vec{r}_b)$ and $2 \text{ e\AA}^{-5}$ in $\nabla^2 \rho(\vec{r}_b)$ at the bond critical points (BCP') and are generally smaller for C–C-bonds. The atomic properties (see chapter 3.2.2) of the non-hydrogen atoms show the same stability, the V_{001} shift is below $0.3 \text{ \AA}^3$ for all atoms and the shift in the charges only exceeds 0.05 e in the cases of C(29) and C(71). For this reason and for reasons of clarity Tables 2, 3 (bond and ring properties) and 4 (atomic properties) only show results of the model *var* compared to theoretical calculation. The influence of the two models to the atomic properties and the thermal displacements of the hydrogen atoms will be discussed in chapter 3.2.3, together with the topology of the X–H bonds and the HB's. A full list of experimental atomic properties of both models is given in the supplementary material as well as static deformation densities of the quinazoline fragment for the theoretical and experimental results.

3.2.1 Bond topology

The general bond topology (Table 2) is as expected, so the experimental results can be discussed in a qualitative way. For all bonds between sp^3 -hybridized atoms the following results were found: C–C bonds have $\rho(\vec{r}_b)$ -values around $1.67 \text{ e\AA}^{-3}$, C–N and C–O single bonds vary between 1.70 and $1.83 \text{ e\AA}^{-3}$, all Laplacians of the bonds between sp^3 -hybridized atoms are close to $-11 \text{ e\AA}^{-5}$. The values of the two bonds O(6)–C(6) and O(7)–C(7) connecting the aromatic quinazoline system with the aliphatic side chains (ca. $1.36 \text{ \AA}$, $2.07 \text{ e\AA}^{-3}$ and $-20 \text{ e\AA}^{-5}$) lie in between the values expected for C=O double bonds (ca. $1.22 \text{ \AA}$, $2.86 \text{ e\AA}^{-3}$ and $-36 \text{ e\AA}^{-5}$) [21] and C–O single bonds (ca. $1.44 \text{ \AA}$, $1.75 \text{ e\AA}^{-3}$ and $-11 \text{ e\AA}^{-5}$).

Table 2: Topological properties at bond critical points.

Since more than one mesomeric structure can be formulated for the heteroaromatic ring systems the assignment of single or double bonds is ambiguous. Nevertheless bond lengths and $\rho(\vec{r}_b)$ -values at the BCP's reflect the distribution of formal single and double bonds given in Fig. 1 so that this form can be considered as the preferred one. For formal C=C and C-C bonds the averages for $\rho(\vec{r}_b)$ are 2.11(6) and 1.98(8) eÅ⁻³, for N=C and N-C these quantities are by 0.2-0.3 eÅ⁻³ higher: 2.38(5)/2.19(5) eÅ⁻³. The bonds C(9)-C(10) and C(18)-C(19), connecting the two rings in each heteroaromatic fragment, do not fit into this pattern. They should have the character of a bond with bond order (BO) greater than 1.5 concerning the supposed mesomeric structure, but have the bond length of a bond with BO < 1.5 and a small value for the electron density (ca. 2.0 eÅ⁻³). In a study of L-PHE [21] a mean value of 2.19 eÅ⁻³ was found for the bonds in the phenylic system, which has a formal bond order of 1.5. Because this can be detected in both aromatics and is even found in an earlier study of L-TRP [22] and in nucleotides [23] it is obviously no effect of the halogenation in the indole fragment. Of course these effects are not very pronounced, because Lewis-structures do not describe the electronic 'reality', and the results can in parts be influenced by uncertainties of the measurement.

For the methoxyl and propoxyl-morpholine substituents the formal O-C single bonds next to the quinazoline fragment have the expected higher bond strength, expressed by $\rho(\vec{r}_b)$ -values > 2.0 eÅ⁻³. All further bonds show the expected topological descriptors of pure single bonds.

The C-F bond (length 1.3573(5) Å) is somewhat longer than the comparable C_{sp2}-F bonds in pentafluorobenzoic acid (PFBA, 1.32-1.33 Å) [24]. Consequently the $\rho(\vec{r}_b)$ -value of 1.80(3) eÅ⁻³ is lower than in PFBA (2.00-2.12 eÅ⁻³).

The topology of the Cl(15)-C(15) bond will be discussed in chapter 4, based on the consideration of a variety of radial function sets.

Table 2 lists also the bond topological descriptors obtained from theoretical calculation to allow a comparison with experimental results. The agreement/disagreement is rather differently if the C-O, C-N and C-C bonds are considered separately. The positions of the bond critical points, expressed in d₁ (distance of the BCP from the first atom in Table 2) disagree between experiment and theory by 0.10 Å (average) for the six C-O bonds, by 0.07 Å for the nine C-N bonds and by only 0.02 Å for the twenty C-C bonds. Accordingly, the average experimental-theory differences for $\rho(\vec{r}_b)$ and $\nabla^2 \rho(\vec{r}_{rep})$ are largest for the C-O bonds: 0.12 eÅ⁻³ and 5.2 eÅ⁻⁵ and smallest for the C-C bonds: 0.02 eÅ⁻³ and 3.0 eÅ⁻⁵, while the differences for C-N are in between: 0.06 eÅ⁻³ and 3.3 eÅ⁻⁵. These results support the usual findings that for heteroaromatic bonds the difference between experiment and theory is larger than, for example, for C-C bonds [25]-[27]. Nevertheless, since even the uncertainty range for experimental $\rho(\vec{r}_b)$ and $\nabla^2 \rho(\vec{r}_{rep})$ values is dis-

cussed to be around $0.1 \text{ e}\text{\AA}^{-3}$ and $2.5 \text{ e}\text{\AA}^{-5}$, respectively, [28] the agreement between the experimental and theoretical bond topological properties in the present study is reasonable.

Table 3 shows the differences of experiment and theory in terms of ring critical points (RCP's). The general agreement is quite satisfactory. The theoretical values are generally smaller for $\rho(\vec{r}_{rcp})$ and bigger for $\nabla^2 \rho(\vec{r}_{rcp})$. As expected a correlation between ring size and topological parameters can be detected: smaller rings have higher values in $\rho(\vec{r}_{rcp})$ and $\nabla^2 \rho(\vec{r}_{rcp})$. No distinct effects of hetero-atoms in the rings (RCP-2) or of substitution (RCP-4) were found, see Fig. 2.

Table 3: Topology at the ring critical points.

3.2.2 Atomic properties

Making use of the zero-flux surfaces [29], [30] the electron density gradient vector field $\nabla \rho(\vec{r}_b)$ subdivides the three-dimensional space into submolecular partitions. The numeric results of the integration of both the experimental (model *var*) and theoretical data are summarized in Table 4. The quantity V_{001} is based on a cutoff of $\rho = 0.001$ atomic units (au), which is commonly used in theoretical calculations of isolated molecules and therefore allows a comparison of the experimental findings with theory. A criterion for the quality of the integration is a total charge close to zero ($-0.03/0.04 \text{ e}$ for experiment/theory) and a total volume close to the volume of the asymmetric unit ($569.66/567.47 \text{ \AA}^3$ for asymmetric unit/total volume). A list including also total volumes (V_{tot}) and total charges (Q_{tot}) for both experimental integrations is given in the supplementary material.

Table 4: Atomic properties of the model *var* compared to theory at the B3LYP/6-311++G** level.

With few exceptions the charge separations obtained by theory for the non-hydrogen atoms are more pronounced than the experimental ones, but for the hydrogen atoms the opposite holds. Disregarding this systematical difference all charges in the theoretical and in the experimental model follow a comparable trend. Carbon atoms connected to fluorine, oxygen or nitrogen atoms are strongly positive polarized, carbon atoms exclusively bonded to carbon have charges close to zero, independently from the hybridization state. Volkov found that the number of hydrogen atoms being bonded to the carbon atom has more influence to the atomic properties than its state of hybridization [11]. This is confirmed in the present case with respect to the atoms C(21)···C(29) (two H atoms bonded) and C(71) (three H atoms bonded).

The same trends are found for the atomic volumes for which carbon is known to exist in a large volume range [31]. Volumes of sp^3 -hybridized carbon atoms vary between 7.0 and $8.7 \text{ \AA}^3$, sp^2 -C's connected to F, O or N-atoms vary between 8.2 and $9.9 \text{ \AA}^3$ and sp^2 -C's exclusively bonded to carbon atoms have volumes between 10.1 and $11.9 \text{ \AA}^3$. The volumes found in this study agree well with the corresponding ones [31] in cyclohexane ($V_{001} = 8.5 \text{ \AA}^3$)

and benzene ($V_{001} = 12.3 \text{ \AA}^3$). In case of the N-atoms the sp^3 -hybridized N(24) is ca. $4.5 \text{ \AA}^3$ smaller than the sp^2 -nitrogen atoms.

Table 2 reveals one reason for the differences between bond topological and atomic properties in experiment and theory. As mentioned before, the distances to the BCP's (d_i) show variations, which are systematical at the bonds to atoms beyond carbon. For these atoms (Cl, F, O and N) the distance to the BCP is generally larger, which leads to a different partitioning of the atoms and hence to different atomic properties. Therefore the atoms beyond carbon have larger volumes in theory in a range of 0.5 to $4.0 \text{ \AA}^3$, which goes hand in hand with bigger charges. The atomic properties of the carbon atoms are much closer to the theoretically predicted ones and show no trends considering different models and theory and are therefore not discussed in detail. The effect of the halogenation cannot unambiguously be determined through examination of bond lengths or even bond topological properties of the indole fragment, because they are quite similar in the title compound and L-TRP (not shown) [22], but can be observed in the atomic properties. Most evident is the decrease of volume for C(15) and C(16) being bonded to chlorine and fluorine, respectively, and the pronounced positive charge for the C(16) atom.

3.2.3 Hydrogen atoms and hydrogen bonds

The influence of the κ and κ' -values of the hydrogen atoms to the X-H-bonds ($X = \text{C}, \text{N}, \text{O}$) was studied. The 1.13/1.29 set (*var*) generally leads to $\rho(\vec{r}_b)$ values, which are 0.02 to $0.05 \text{ e\AA}^{-3}$ smaller than for the 1.20/1.20 set (*def*), so this effect might be considered to be negligible. The shift for the Laplacian only exceeds $2 \text{ e\AA}^{-5}$ in the case of the N(11)-H(11)-bond which is involved in the strongest hydrogen bond (HB) of this system. These changes may be assigned to a mean shift of the BCP in the range of 0.01 to $0.02 \text{ \AA}$ towards the hydrogen atom if the default kappa-values are changed to those suggested by Volkov [11].

A closer view into the atomic properties of the hydrogen atoms reveals some interesting trends. Figure 4 displays the atomic volumes (4a), charges (4b) and thermal displacements (4c) for the two models and theory.

Figure 4: Model effect on the volumes, charges and thermal displacements of the hydrogen atoms.

A pronounced increase of the hydrogen atomic volumes in the *var* model ($\kappa = 1.13$ and $\kappa' = 1.29$) is found (Fig. 4a), leading to values much closer to theory, even though the BCP's are slightly shifted to the hydrogen atoms as mentioned above. This effect can be explained by comparing the total volumes of the hydrogen atoms to the V_{001} values for both models (given in the supplementary material). For model *var* the sum of the total volumes is $8.4 \text{ \AA}^3$ larger than for model *def*, which is mainly compensated by a decrease of certain carbon-volumes, but considering the V_{001} values an increase of $15.5 \text{ \AA}^3$ is found. This means that the main effect is not an increase of the Bader-basins but an increase of V_{001} inside these basins. This effect is not seen for H(11), which may be attributed to the close appearance of the oxygen atom O(27) involved in the formation of the me-

dium range HB. The low value of $V_{001}(\text{H}(11))$ is due to the connection to a nitrogen atom, which is more electronegative than carbon, and the participation in the $\text{N}(11)\cdots\text{H}(11)\cdots\text{O}(27)$ hydrogen bond.

The atomic charges of the hydrogen atoms are generally more positive in case of being bonded to aromatic carbon (and nitrogen) atoms. This could be expected, since with increasing s-character (sp^2 instead of sp^3) the electronegativity of carbon atoms increases, too. Figure 4b shows that the charge description of the methyl hydrogen atoms (last three columns) is much less appropriate than for all other hydrogen atoms, which may be explained with the rotational freedom of the methyl group, which is not limited by sterical reasons. Diagram 4c reveals that the ADP's decrease (as the volumes increase) for all hydrogen atoms through introduction of the 1.13/1.29 set.

Because all HB's (also the weak $\text{C-H}\cdots\text{F}$ contacts) follow exactly the predictions given in the literature [32]–[36] in terms of $\rho(\vec{r}_b)$, $\nabla^2\rho(\vec{r}_b)$, λ_3 , $G(\vec{r}_b)$, $V(\vec{r}_b)$, $G(\vec{r}_b)/V(\vec{r}_b)$, $H(\vec{r}_b)$ and E_{HB} and because only non weak intermolecular contact exists in the crystalline environment, the topology of the HB-pattern is not discussed here in detail. No distinct effect of the model was observed. The two tables carrying all topological information of model *var* are given in the supplementary material. Interestingly the HB-energies (Table A.3) calculated from the topological data following Abramov [37] are close to those arising from a formula just including the geometry [32], with one exception: The internal HB between H(14) and N(3) is suggested to be much weaker using the geometrical criteria only.

3.2.4 Electrostatic potential

The electrostatic potential (ESP), calculated from the experimental data using the method of Su and Coppens [38], shows an extended range of weak negative potential above and below both aromatic ring systems (Figure 5), which shields large parts of the molecule from interactions to the equally charged regions at the receptor site.

Figure 5: Electrostatic potential of the title compound, generated with the XDGRAPH module of the XD package. Negative values (mesh representation) at $-0.05 \text{ e}\text{\AA}^{-1}$, positive values (dark grey surface) at $1.5 \text{ e}\text{\AA}^{-1}$. The effect of the π -electron distribution on both sides of the aromatic systems is shown.

4. The Cl-C-bond

To overcome the shortcomings of the standard model [25]–[27] one can refine individual κ' for each spherical harmonic against the theoretical structure factors [39] of model compound (III), which leads to a better description of the bond. Additionally one can examine different n_l sets ($l = 1-4$) for the radial functions of the spherical harmonics. Several publications appeared attempting to find optimal n_l -sets for aluminium, silicon, phosphorus and sulfur [40 and references therein, 41]. 15 n_l -sets (1234, 2345, 3456, 4567, 5678, 4444, 5555, 6666, 7777, 8888, 2468, 4468, 5566, 6677 and 6688 for $l = 1-4$) have been tested in this study. The effect of the n_l -sets to the behaviour of the Laplacian

along the Cl(15)-C(15) bond in theory and experiment was studied.

A 5-step approach was considered as described below, a summary of results is given in Tables 5 and 6.

Step 1: The above introduced model compound 5-fluoro-6-chloro-indole (III) was used for a multipole refinement of its theoretical structure factors using various n_l -sets (see Table 5, part A). κ and κ' were set equal to 1 and kept constant.

Step 2: Model compound (III) as in step 1, but κ , κ' refined for Cl(15) and C(15), κ' equal for all n_l (keep k'), see Table 5, part B.

Step 3: Model compound (III) as above, κ and individual $\kappa'_1 - \kappa'_4$ refined for Cl, Table 5, part C.

Step 4: Assignment of κ , κ' values from step 2 to the experimental data of the title compound (IIa), Table 6, part D.

Step 5: Assignment of the individual $\kappa'_1 - \kappa'_4$ from step 3 to the experimental data of (IIa), Table 6, part E.

For step 1 the results for all n_l -sets are shown in Table 5, part A in terms of R-value, max/min residual density and topological descriptors of the C-Cl-bond. The latter ones will be compared with the corresponding theoretical quantities (theo data) obtained for the complete title molecule (see part F in Table 6).

It can be seen that within blocks 1 and 2, (4444-8888 and 1234-5678) the n_l -sets (4444) and (3456) seem to perform best in their corresponding blocks. For (3456) $\rho(\vec{r}_b)$ values are higher and $\nabla^2 \rho(\vec{r}_b)$ and λ_3 are lower, coming similarly close to the theo data like the (2468)-set, which was identified to be the optimum choice for sulfur [40]. In block 1 (8888) has the smallest λ_3 -value. Generally all n_l -sets with different integers for all l are closer to the theo data.

Table 5: XD refinement of the theoretical data of model compound (III). Section A: Refinement following step 1 as described in the text, section B: step 2, section C: step3.

Table 6: XD refinement of the experimental data with assignment of theoretically obtained κ and κ' -values. Section D: Refinement following step 4 as described in the text, section E: step 5. Section F: Theoretical results (B3LYP/6-31G**).

The three models (4444, 3456, 2468) already favored in step 1 have κ' -values close to 1.0 after the κ' refinement in step 2 (see Table 5, part B), indicating a quite good starting model given by the n_l -sets. After κ' -refinement the data show only slight variations (part B), because nearly all initial differences between the different n_l -sets are balanced (which is known from literature [40]). But the adjustment to a 'final' bond topology is not total so that all parameters show a small increase/decrease with increasing n_l -values. For the first block the introduction of different $\kappa'_1 - \kappa'_4$ for the n_l 's via unconstrained κ' refinement (Table 5, part C) leads to an improvement of the fit.

Because of the mentioned balance the examination of R_F and of the residual densities for the assignment of κ and κ' -values to the experimental data (steps 4 and 5, Table 6, part D and E) does not lead to an unambiguous way to judge the quality of the n_l -choices. Indeed, the n_l -sets including dif-

fuse functions (8888 and 5678) have the smallest residual densities within their blocks, but the 2468-set, which emerged as the model with the best fit concerning bond topological properties, has the highest of all sets tested. Considering the topological properties $\rho(\vec{r}_b)$, $\nabla^2 \rho(\vec{r}_b)$, λ_3 and d_1 those sets already known [40] to lead to superior fits of the bonds to second row elements (2468, 4468, 6677, 6688) and the new set 5678 show the closest vicinity to the theoretical data. But since the latter 4 sets include κ'_1 -values greater than 1.5 the use of the 2468-set seems to be preferable ($\kappa'_1 - \kappa'_4 = 1.09, 1.05, 1.09, 1.37$). Interestingly the best sets have κ' -values close to or greater than one, which means a contraction of the valence shells.

Because the results summarized in Table 5 and 6 prove to be quite insensitive parameters to the quality of the modeling of the bond to the chlorine atom, the examination of the distribution of the Laplacian along the C-Cl bond (Figure 6) may identify some sets to be superior to others.

Figure 6: Dependency of the Laplacian along the Cl(15)-C(15)-bond in terms of different refinement steps. First row: step 1 procedure for blocks 1-3 (see Table 5), second row: step 2, third row: step 3.

Figure 6 (plots A1-A3) shows the resulting Laplacians according to step 1 for the three n_I -blocks 1-3 (see Table 6). The plots B1-B3 gives the corresponding Laplacians according to the κ -treatment in step 2. It can be seen that the κ -refinement balances the differences caused by the chosen n_I -sets (as shown in plots A1-A3) to yield Laplacians of very similar shape. However, in plot B1 (n_I -sets 4444-8888) the Laplacian at the BCP is less negative compared to plots B2 and B3. After introduction of individual κ'_1 - κ'_4 -values (step 3, plots C1-C3), the Laplacians show different behaviour for block 1 and 2 (plot C1 and C2), but not for block 3 (plot C3). There is a tendency that Laplacians showing the smallest changes when going from step 1 to step 3 correspond to κ' -values close to one.

The step 4 and step 5 assignments to the experimental data yield Laplacians as illustrated in Fig. 7. Interestingly the Laplacians obtained by assignment of κ , κ' -values as described in step 4 show a rather strong variation in shape which confirms previous findings that the n_I -ratios have more influence than their absolute values. The strong variations are reduced in the step 5 procedure.

Figure 7: Laplacian along the Cl(15)-C(15)-bond after assignment of theoretically obtained κ' and κ' -values. D: step 4 procedure, E: step 5.

5. Conclusion

In this study the optimization of the radial expansion of the chlorine atom within the single-zeta approach via the application of 15 different n_I -sets yield 2468 to be the best one. The examination of bond topological properties, especially the curvature along the Cl-C bond seems to be a proper tool to judge the quality of the fit.

Finally the use of 1.13 and 1.29 for κ and κ' of the hydrogen atoms, as suggested by Volkov [11] leads to atomic volumes of the hydrogen atoms much closer to theory and simultaneously to smaller thermal displacements.

Regarding the already mentioned problem that no binding study of an indole quinazoline with the corresponding receptor is known, pharmaceutical implications from the electronic structure of the title compound would be rather speculative. However, one may conclude that also in biological environment the selective properties of this class of inhibitors are caused by the disability to build strong intermolecular interactions in combination with the effect of the electrostatic potential. It is mainly dominated by rather large regions of diffuse negative potential on top and below the aromatic systems (Fig. 5), so that major parts of the molecule are hindered from interacting with equally charged binding sites of any potential receptor.

Figure 1: Substituted 4-anilino-quinazoline (I) and 4-(indol-3-yl)-quinazoline (II). R1-R4: variable residues. Model compound 5-chloro-6-fluoro-indol (III), see chapter 2.2.

Figure 2: ORTEP-plot [19] of the title compound (IIa). Probability at 50%.

Figure 3: SCHAKAL-representation [20] of the dimer formed via the strongest hydrogen bond of the title complex.

Figure 4: Effect of the model on the volumes (a), charges (b) and thermal displacements (c) of the hydrogen atoms.

Figure 5: Electrostatic potential of the title complex, generated with the XDGRAPH module of the XD package. Negative values (mesh representation) at $-0.05 \text{ e}\text{\AA}^{-1}$, positive values (dark grey surface) at $1.5 \text{ e}\text{\AA}^{-1}$. The effect of the π -electron distribution on both sides of the aromatic systems is shown.

Figure 6: Dependency of the Laplacian along the Cl(15)-C(15)-bond in terms of different refinement steps. First row: step 1 procedure for blocks 1-3 (see Table 5), second row: step 2, third row: step 3.

Figure 7: Laplacian along the Cl(15)-C(15)-bond after assignment of theoretically obtained κ' and κ'' -values. D: step 4 procedure, E: step 5.

Table 1: Crystallographic data and experimental conditions for (IIa)

Empirical formula	C ₂₄ H ₂₄ ClFN ₄ O ₃
Formular weight [g mol ⁻¹]	470.92
Crystal system	monoclinic
Space group (no.)	P2 ₁ /c (14)
Z	4
Temperature [K]	100
a, b, c [Å]	13.653(3), 15.770(3), 11.346(2)
β [°]	111.13(3)
V [Å ³]	2278.7(9)
Calculated density [g cm ⁻³]	1.37
F(000)	984
Crystal form	needle
Crystal size [mm]	0.4 x 0.2 x 0.2
λ [Å]	0.56, synchrotron
$\sin\theta/\lambda_{\max}$ [Å ⁻¹]	1.11
No. of collected reflections	470587
Symmetry independent	26097
Included in the refinement (I > 3 σ ; N _{ref})	15784
No. of variables (N _{var})	794
Completeness [%]	99.9

Redundancy	18.0
$R_{\text{int}}(F^2)$ [%]	9.42
R_1 (spherical) [%]	3.02
$R_F(F)$, $R_{\text{all}}(F)$, $R_w(F)$ [%]	1.84, 3.32, 2.57
$R_F(F^2)$, $R_{\text{all}}(F^2)$, $R_w(F^2)$ [%]	2.93, 3.15, 5.07
GoF	0.42
$N_{\text{ref}}/N_{\text{var}}$	19.9
$\Delta\rho_{\text{min}}$, $\Delta\rho_{\text{max}}$ /eÅ ⁻³	-0.341, 0.344

Table 2: Topological properties at bond critical points (exp: model var)

Bond	d [Å]		$d_{\text{I}}[\text{Å}]$		$\rho(\vec{r}_b)$ [eÅ ⁻³]		$\nabla^2\rho(\vec{r}_b)$ [eÅ ⁻⁵]		ϵ	
	exp.		exp.	calc.	exp.	calc.	exp.	calc.	exp.	calc.
Cl(15) - C(15)	1.7439(3)		0.9904	0.9998	1.30(2)	1.33	-1.8(1)	-6.9	0.08	0.06
F(16) - C(16)	1.3573(5)		0.8425	0.8999	1.80(3)	1.69	-16.4(2)	2.6	0.11	0.01
O(6) - C(6)	1.3629(4)		0.8070	0.8954	2.08(3)	1.93	-18.5(1)	-10.1	0.05	0.04
O(6) - C(21)	1.4484(4)		0.8267	0.9370	1.70(3)	1.60	-9.1(1)	-8.9	0.06	0.04
O(7) - C(7)	1.3589(4)		0.8242	0.8917	2.05(3)	1.97	-22.5(2)	-9.8	0.16	0.03
O(7) - C(71)	1.4370(5)		0.8271	0.9357	1.77(3)	1.63	-13.0(1)	-7.9	0.03	0.01
O(27) - C(26)	1.4387(6)		0.8074	0.9203	1.72(3)	1.67	-8.8(1)	-11.9	0.05	0.03
O(27) - C(28)	1.4322(7)		0.8242	0.9218	1.81(2)	1.64	-13.4(1)	-11.7	0.02	0.03
N(1) - C(2)	1.3231(4)		0.7611	0.8296	2.43(3)	2.39	-25.5(2)	-24.5	0.16	0.16
N(1) - C(9)	1.3696(4)		0.7834	0.8284	2.19(3)	2.17	-19.6(1)	-23.2	0.09	0.09
N(3) - C(2)	1.3560(4)		0.7802	0.8345	2.25(3)	2.25	-20.4(1)	-24.0	0.19	0.11
N(3) - C(4)	1.3462(4)		0.7434	0.8246	2.33(3)	2.27	-19.6(1)	-24.3	0.21	0.13
N(11) - C(12)	1.3765(4)		0.7860	0.8788	2.10(3)	2.06	-15.3(1)	-17.1	0.36	0.15
N(11) - C(18)	1.3816(4)		0.7674	0.8797	2.21(3)	2.01	-19.7(1)	-17.7	0.21	0.13
N(24) - C(23)	1.4717(5)		0.8118	0.8642	1.75(3)	1.77	-10.0(1)	-15.9	0.05	0.06
N(24) - C(25)	1.4667(4)		0.8004	0.8630	1.83(2)	1.74	-11.9(1)	-15.2	0.06	0.05
N(24) - C(29)	1.4672(5)		0.8017	0.8608	1.83(2)	1.78	-12.1(1)	-16.2	0.03	0.06
C(4) - C(10)	1.4360(4)		0.7365	0.7260	1.96(2)	1.95	-16.6(1)	-18.2	0.16	0.18
C(4) - C(13)	1.4677(4)		0.7340	0.7349	1.84(2)	1.86	-12.2(1)	-17.3	0.13	0.12
C(5) - C(6)	1.3846(4)		0.6840	0.6607	2.17(2)	2.13	-19.3(1)	-21.0	0.28	0.30
C(5) - C(10)	1.4318(4)		0.7023	0.7163	1.91(2)	1.91	-13.2(1)	-17.5	0.08	0.17
C(6) - C(7)	1.4483(4)		0.7212	0.7200	1.99(2)	1.96	-15.2(1)	-19.0	0.25	0.22
C(7) - C(8)	1.3820(4)		0.7032	0.7273	2.15(2)	2.12	-17.8(1)	-21.0	0.25	0.29
C(8) - C(9)	1.4236(4)		0.7059	0.7051	1.98(2)	2.00	-16.2(1)	-19.5	0.17	0.19
C(9) - C(10)	1.4249(4)		0.7166	0.7129	2.00(2)	2.02	-16.6(1)	-19.5	0.17	0.18
C(12) - C(13)	1.3925(4)		0.7099	0.7224	2.12(2)	2.08	-17.6(1)	-19.8	0.30	0.32
C(13) - C(19)	1.4536(4)		0.7432	0.7226	1.83(2)	1.86	-12.1(1)	-16.4	0.15	0.17
C(14) - C(15)	1.3917(4)		0.6890	0.6681	2.11(2)	2.10	-17.5(1)	-20.5	0.25	0.27
C(14) - C(19)	1.4096(4)		0.7173	0.7005	2.05(2)	2.00	-17.5(1)	-19.1	0.15	0.19
C(15) - C(16)	1.4145(5)		0.6986	0.6916	2.07(2)	2.05	-17.0(1)	-19.9	0.37	0.30
C(16) - C(17)	1.3863(5)		0.7536	0.7256	2.16(3)	2.11	-18.7(1)	-20.9	0.23	0.32
C(17) - C(18)	1.4049(4)		0.7291	0.6841	2.05(2)	2.03	-16.6(1)	-19.7	0.25	0.23
C(18) - C(19)	1.4215(4)		0.7246	0.7334	2.03(2)	2.04	-16.3(1)	-19.9	0.26	0.21
C(21) - C(22)	1.5254(4)		0.8062	0.7826	1.68(2)	1.66	-12.8(1)	-13.9	0.02	0.04
C(22) - C(23)	1.5390(5)		0.7422	0.7620	1.62(2)	1.62	-10.6(1)	-13.0	0.06	0.02
C(25) - C(26)	1.5289(7)		0.7493	0.7625	1.66(2)	1.69	-10.5(1)	-14.2	0.03	0.02
C(28) - C(29)	1.5314(7)		0.7813	0.7663	1.66(2)	1.68	-10.4(1)	-14.2	0.03	0.02

Table 3: Topology of the ring critical points*

	$\rho(\vec{r}_b)$ [eÅ ⁻³]	$\nabla^2 \rho(\vec{r}_b)$ [eÅ ⁻⁵]	$\emptyset_{\text{ring}}$ [Å]	λ_1	λ_2	λ_3
1	0.37(1)	7.0(1)	ca. 2.4	-1.07	3.45	4.67
	0.33	8.1		-1.23	4.53	4.76
2	0.20(1)	3.5(1)	ca. 2.9	-0.53	1.79	2.20
	0.17	4.2		-0.51	2.24	2.45
3	0.19(1)	2.8(1)	ca. 2.8	-0.44	1.44	1.78
	0.14	3.1		-0.36	1.47	1.98
4	0.18(1)	3.0(1)	ca. 2.8	-0.35	1.60	1.74
	0.14	3.6		-0.36	1.89	2.04
5	0.19(1)	2.7(1)	ca. 2.9	-0.53	1.45	1.74
	0.13	3.4		-0.34	1.79	1.99
6	0.08(1)	1.1(1)	ca. 3.1	-0.17	0.21	1.05
	0.07	1.2		-0.15	0.23	1.11

* First/second row: experimental/theoretical results

Table 4: Atomic properties of the model *var* compared to theory at the B3LYP/6-311++G**⁻-level.

atom	V_{001} [Å ³]		Q_{001} [e]		atom	V_{001} [Å ³]		Q_{001} [e]	
	exp.	calc.	exp.	calc.		exp.	calc.	exp.	calc.
Cl(15)	30.98	32.06	-0.01	-0.10	C(26)	8.47	7.67	0.35	0.48
F(16)	14.90	16.01	-0.54	-0.58	C(28)	8.70	7.70	0.35	0.47
O(6)	13.74	14.43	-0.82	-1.03	C(29)	7.89	7.54	0.17	0.35
O(7)	13.81	14.58	-0.80	-1.03	C(71)	8.24	8.55	0.59	0.52
O(27)	13.12	15.36	-0.71	-0.99	H(2)	6.36	7.05	0.04	0.07
N(1)	13.99	17.96	-0.76	-1.09	H(5)	4.87	5.97	0.07	0.04
N(3)	15.37	16.79	-0.74	-1.08	H(8)	6.28	6.55	0.07	0.07
N(11)	14.28	15.41	-0.95	-1.16	H(11)	3.16	4.43	0.48	0.43
N(24)	9.92	11.80	-0.64	-0.94	H(12)	6.42	6.86	0.12	0.08
C(2)	9.81	8.86	0.82	1.01	H(14)	6.80	6.33	0.06	0.11
C(4)	9.26	8.93	0.28	0.50	H(17)	6.92	7.13	0.10	0.08
C(5)	11.32	12.20	-0.09	-0.01	H(21A)	6.08	7.13	-0.04	0.03
C(6)	8.44	9.06	0.35	0.51	H(21B)	6.61	6.95	-0.04	0.02
C(7)	8.93	9.01	0.40	0.52	H(22A)	6.46	7.20	-0.02	0.04
C(8)	11.27	12.47	-0.02	-0.04	H(22B)	6.91	7.20	-0.02	0.02
C(9)	8.80	8.96	0.36	0.44	H(23A)	7.72	7.75	-0.02	0.00
C(10)	10.10	10.61	-0.03	-0.01	H(23B)	6.35	7.14	-0.03	0.01
C(12)	10.69	11.16	0.11	0.40	H(25A)	6.31	7.00	0.03	0.02
C(13)	9.68	10.70	-0.06	0.01	H(25B)	7.50	7.63	0.03	0.01
C(14)	11.90	11.87	-0.04	0.04	H(26A)	7.41	7.18	0.03	0.05
C(15)	9.88	10.60	0.01	0.09	H(26B)	7.11	7.54	0.05	0.01
C(16)	8.22	9.26	0.44	0.52	H(28A)	7.82	7.18	0.05	0.05
C(17)	11.33	12.67	-0.02	0.01	H(28B)	7.43	7.47	0.04	0.02
C(18)	9.21	9.30	0.23	0.38	H(29A)	7.03	7.19	0.02	0.02
C(19)	9.60	10.48	0.00	0.01	H(29B)	7.53	7.72	0.03	0.00
C(21)	7.00	7.22	0.35	0.47	H(71A)	7.88	6.93	-0.06	0.03
C(22)	8.04	8.35	0.21	0.07	H(71B)	8.13	6.98	-0.06	0.03
C(23)	7.72	7.48	0.23	0.34	H(71C)	7.29	6.91	-0.06	0.05
C(25)	7.85	7.69	0.24	0.32					

Table 5: XD refinement of the theoretical data of model compound (III). Section A: Refinement following step 1 as described in the text, section B: step 2, section C: step3.

block	n _i - set	R _F [%]	Δρ _{min} [eÅ ⁻³]	Δρ _{max} [eÅ ⁻³]	ρ($\vec{r}_b$) [eÅ ⁻³]	∇ ² ρ($\vec{r}_b$) [eÅ ⁻⁵]	d ₁ [Å]	λ ₃	κ	κ'	κ	κ' ₁	κ' ₂	κ' ₃	κ' ₄
A															
1	4444	0.42	-0.041	0.041	1.25(1)	-1.5(1)	0.9669	12.48							
	5555	0.43	-0.043	0.049	1.25(1)	-1.5(1)	0.9736	12.57							
	6666	0.45	-0.045	0.057	1.25(1)	-1.5(1)	0.9849	12.27							
	7777	0.47	-0.046	0.060	1.25(1)	-1.5(1)	0.9942	11.62							
	8888	0.49	-0.046	0.063	1.24(1)	-1.5(1)	0.9959	11.02							
2	1234	0.44	-0.042	0.042	1.25(1)	-1.2(1)	0.9870	12.45							
	2345	0.42	-0.041	0.041	1.27(1)	-2.0(1)	0.9827	12.04							
	3456	0.41	-0.040	0.041	1.27(1)	-2.5(1)	0.9739	11.69							
	4567	0.43	-0.043	0.049	1.26(1)	-2.1(1)	0.9682	11.69							
	5678	0.46	-0.045	0.056	1.24(1)	-1.3(1)	0.9703	11.88							
3	2468	0.41	-0.040	0.040	1.27(1)	-2.7(1)	0.9701	11.01							
	4468	0.41	-0.042	0.041	1.27(1)	-2.6(1)	0.9689	11.09							
	5566	0.43	-0.044	0.051	1.26(1)	-2.0(1)	0.9734	11.86							
	6677	0.46	-0.045	0.057	1.25(1)	-1.6(1)	0.9778	11.78							
	6688	0.46	-0.046	0.057	1.23(1)	-1.0(1)	0.9661	11.86							
B															
1	4444	0.27	-0.015	-0.019	1.25(1)	-1.2(1)	0.9688	12.53	1.00	0.92	1.01	0.98			
	5555	0.28	-0.015	-0.019	1.25(1)	-1.3(1)	0.9687	12.49	1.00	0.91	1.01	1.16			
	6666	0.28	-0.015	-0.018	1.25(1)	-1.3(1)	0.9688	12.44	1.00	0.91	1.01	1.35			
	7777	0.28	-0.016	-0.018	1.25(1)	-1.4(1)	0.9689	12.40	1.00	0.91	1.01	1.53			
	8888	0.28	-0.017	-0.018	1.24(1)	-1.4(1)	0.9690	12.36	1.00	0.91	1.01	1.72			
2	1234	0.26	-0.013	-0.015	1.26(1)	-1.6(1)	0.9763	12.04	1.00	0.94	1.01	0.68			
	2345	0.26	-0.013	-0.015	1.26(1)	-1.9(1)	0.9763	11.95	1.00	0.93	1.01	0.85			
	3456	0.26	-0.013	-0.015	1.26(1)	-2.0(1)	0.9768	11.88	1.00	0.92	1.01	1.03			
	4567	0.26	-0.013	-0.015	1.27(1)	-2.2(1)	0.9776	11.84	1.00	0.92	1.01	1.21			
	5678	0.27	-0.013	-0.015	1.27(1)	-2.3(1)	0.9785	11.81	1.00	0.92	1.01	1.39			
3	2468	0.26	-0.013	-0.015	1.27(1)	-2.4(1)	0.9812	11.38	1.00	0.94	1.01	1.09			
	4468	0.27	-0.013	-0.016	1.27(1)	-2.4(1)	0.9794	11.40	1.00	0.94	1.01	1.10			
	5566	0.27	-0.013	-0.015	1.26(1)	-1.9(1)	0.9768	12.06	1.00	0.92	1.01	1.21			
	6677	0.27	-0.014	-0.015	1.26(1)	-2.0(1)	0.9773	12.05	1.00	0.92	1.01	1.39			
	6688	0.27	-0.014	-0.014	1.27(1)	-2.6(1)	0.9843	11.58	1.00	0.93	1.01	1.45			
C															
1	4444	0.26	-0.013	-0.015	1.27(1)	-2.1(1)	0.9783	11.68	1.00	0.92	1.01	1.56	1.06	0.80	0.77
	5555	0.26	-0.013	-0.015	1.27(1)	-2.4(1)	0.9812	11.45	1.00	0.91	1.01	1.83	1.26	0.93	0.91
	6666	0.26	-0.013	-0.015	1.28(1)	-2.8(1)	0.9842	11.25	1.00	0.91	1.01	2.10	1.46	1.07	1.04
	7777	0.26	-0.013	-0.014	1.28(1)	-3.0(1)	0.9873	11.08	1.00	0.91	1.01	2.36	1.67	1.21	1.18
	8888	0.26	-0.013	-0.014	1.28(1)	-3.3(1)	0.9905	10.95	1.00	0.91	1.01	2.63	1.87	1.35	1.31
2	1234	0.26	-0.013	-0.016	1.26(1)	-1.7(1)	0.9762	12.14	1.00	0.94	1.01	0.80	0.66	0.67	0.81
	2345	0.26	-0.013	-0.016	1.26(1)	-2.0(1)	0.9781	11.89	1.00	0.93	1.01	1.06	0.85	0.81	0.94
	3456	0.26	-0.013	-0.015	1.27(1)	-2.3(1)	0.9806	11.64	1.00	0.92	1.01	1.33	1.05	0.94	1.07
	4567	0.26	-0.013	-0.015	1.28(1)	-2.6(1)	0.9834	11.42	1.00	0.92	1.01	1.59	1.26	1.08	1.20
	5678	0.26	-0.013	-0.014	1.28(1)	-2.9(1)	0.9863	11.22	1.00	0.92	1.01	1.85	1.46	1.22	1.33
3	2468	0.26	-0.013	-0.015	1.28(1)	-2.4(1)	0.9827	11.64	1.00	0.94	1.01	1.09	1.05	1.09	1.37
	4468	0.26	-0.013	-0.015	1.28(1)	-2.5(1)	0.9830	11.61	1.00	0.94	1.01	1.57	1.05	1.09	1.37
	5566	0.26	-0.013	-0.015	1.28(1)	-2.6(1)	0.9830	11.42	1.00	0.92	1.01	1.83	1.26	1.08	1.06
	6677	0.26	-0.013	-0.014	1.28(1)	-2.9(1)	0.9860	11.23	1.00	0.92	1.01	2.10	1.46	1.22	1.19
	6688	0.26	-0.013	-0.014	1.28(1)	-3.0(1)	0.9878	11.22	1.00	0.93	1.01	2.10	1.46	1.36	1.33

Table 6: XD refinement of the experimental data with assignment of theoretically obtained κ and κ' -values. Section D: Refinement following step 4 as described in the text, section E: step 5. Section F: Theoretical results (B3LYP/6-31G**).

block	n _i - set	R _F [%]	$\Delta\rho_{\min}$ [eÅ ⁻³]	$\Delta\rho_{\max}$ [eÅ ⁻³]	$\rho(\vec{r}_b)$ [eÅ ⁻³]	$\nabla^2\rho(\vec{r}_b)$ [eÅ ⁻⁵]	d ₁ [Å]	λ_3
D								
1	4444	1.89	-0.352	0.320	1.30(2)	-2.2(1)	0.9945	12.80
	5555	1.89	-0.350	0.320	1.31(2)	-2.1(1)	0.9952	12.92
	6666	1.89	-0.349	0.320	1.31(2)	-2.0(1)	0.9955	13.05
	7777	1.89	-0.348	0.320	1.31(3)	-1.9(1)	0.9955	13.20
	8888	1.89	-0.347	0.320	1.31(3)	-1.8(1)	0.9952	13.34
2	1234	1.89	-0.372	0.333	1.30(2)	-2.6(1)	0.9850	12.04
	2345	1.89	-0.368	0.331	1.31(2)	-2.7(1)	0.9901	12.01
	3456	1.89	-0.363	0.330	1.31(2)	-2.9(1)	0.9944	12.04
	4567	1.89	-0.360	0.329	1.32(2)	-2.9(1)	0.9978	12.13
	5678	1.89	-0.357	0.328	1.32(2)	-2.9(1)	1.0004	12.26
3	2468	1.89	-0.374	0.337	1.31(2)	-3.2(1)	0.9816	11.38
	4468	1.89	-0.360	0.334	1.31(2)	-3.2(1)	0.9932	11.41
	5566	1.89	-0.353	0.323	1.31(2)	-2.7(1)	1.0027	12.43
	6677	1.89	-0.351	0.322	1.32(3)	-2.6(1)	1.0038	12.59
	6688	1.89	-0.353	0.325	1.32(3)	-3.2(1)	1.0091	12.05
E								
1	4444	1.89	-0.366	0.326	1.32(1)	-3.2(1)	0.9865	11.74
	5555	1.89	-0.366	0.326	1.32(1)	-3.5(1)	0.9887	11.51
	6666	1.89	-0.365	0.326	1.33(2)	-3.9(1)	0.9912	11.29
	7777	1.89	-0.365	0.327	1.33(3)	-4.2(1)	0.9939	11.11
	8888	1.89	-0.364	0.327	1.34(3)	-4.4(1)	0.9967	10.96
2	1234	1.89	-0.372	0.326	1.31(2)	-2.9(1)	0.9869	12.11
	2345	1.89	-0.370	0.326	1.32(2)	-3.2(1)	0.9985	11.89
	3456	1.89	-0.369	0.326	1.32(2)	-3.5(1)	0.9904	11.67
	4567	1.89	-0.368	0.327	1.33(2)	-3.8(1)	0.9925	11.45
	5678	1.89	-0.367	0.327	1.33(2)	-4.1(1)	0.9950	11.25
3	2468	1.89	-0.371	0.327	1.33(2)	-3.7(1)	0.9940	11.64
	4468	1.89	-0.367	0.327	1.33(3)	-3.7(1)	0.9937	11.65
	5566	1.89	-0.366	0.326	1.33(2)	-3.7(1)	0.9912	11.47
	6677	1.89	-0.365	0.327	1.33(2)	-4.0(1)	0.9936	11.27
	6688	1.89	-0.366	0.327	1.33(3)	-4.2(1)	0.9960	11.26
F								
	theo				1.33	-6.9	0.9998	7.99

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Supplementary Material

Table S.1: Results of experimental integration of the two different models

atom	V ₀₀₁		V _{tot}		Q _{tot}	
	var	def	var	def	var	def
Cl(15)	30.98	30.67	35.04	37.20	-0.01	-0.06
F(16)	14.90	14.77	16.17	16.82	-0.55	-0.54
O(6)	13.74	13.76	14.59	14.92	-0.82	-0.84
O(7)	13.81	13.86	14.24	14.60	-0.80	-0.81
O(27)	13.12	12.94	14.37	14.81	-0.71	-0.72
N(1)	13.99	14.17	14.54	14.88	-0.76	-0.75
N(3)	15.37	15.24	15.82	16.34	-0.75	-0.76
N(11)	14.28	13.95	15.70	15.76	-0.95	-0.93
N(24)	9.92	9.97	10.01	10.17	-0.64	-0.64
C(2)	9.81	9.66	10.82	11.21	0.82	0.81
C(4)	9.26	9.41	9.26	9.42	0.28	0.23
C(5)	11.32	11.36	11.42	11.63	-0.09	-0.09
C(6)	8.44	8.54	8.45	8.58	0.35	0.32
C(7)	8.93	9.05	9.04	9.23	0.40	0.35
C(8)	11.27	11.20	12.48	12.75	-0.02	-0.02
C(9)	8.80	8.76	9.74	9.95	0.33	0.32
C(10)	10.10	10.12	10.35	10.57	-0.03	-0.06
C(12)	10.69	10.61	11.20	11.47	0.11	0.11
C(13)	9.68	9.77	9.68	9.77	-0.06	-0.08
C(14)	11.90	11.83	12.31	12.44	-0.04	-0.05
C(15)	9.88	9.89	10.02	10.07	0.01	-0.01
C(16)	8.22	8.30	8.22	8.32	0.44	0.39
C(17)	11.33	11.34	11.40	11.43	-0.02	-0.04
C(18)	9.21	9.23	9.48	9.56	0.23	0.19
C(19)	9.60	9.68	9.60	9.68	0.00	-0.04
C(21)	7.00	6.98	7.00	6.98	0.35	0.38
C(22)	8.04	8.04	8.30	8.40	0.21	0.25
C(23)	7.72	7.71	7.77	7.80	0.23	0.27
C(25)	7.85	7.70	8.33	8.33	0.23	0.27
C(26)	8.47	8.33	8.65	8.79	0.35	0.37
C(28)	8.70	8.57	9.18	9.42	0.35	0.37
C(29)	7.89	7.65	8.19	8.14	0.17	0.27
C(71)	8.24	7.76	8.83	8.52	0.59	0.69
H(2)	6.36	5.90	6.60	6.36	0.04	0.07
H(5)	4.87	4.75	4.87	4.78	0.07	0.06
H(8)	6.28	5.73	6.45	6.10	0.07	0.07
H(11)	3.16	3.20	3.30	3.37	0.48	0.44
H(12)	6.42	5.62	7.99	7.66	0.11	0.12
H(14)	6.80	6.05	6.97	6.60	0.06	0.06
H(17)	6.92	5.93	8.43	7.63	0.09	0.09
H(21A)	6.08	5.85	6.08	5.88	-0.04	-0.03
H(21B)	6.61	6.01	6.98	6.64	-0.04	-0.03
H(22A)	6.46	6.18	6.66	6.40	-0.02	-0.01
H(22B)	6.91	6.21	9.14	8.70	-0.02	-0.04
H(23A)	7.72	6.57	9.75	9.35	-0.03	-0.03
H(23B)	6.35	6.06	6.36	6.16	-0.03	-0.04
H(25A)	6.31	5.93	7.14	6.87	0.02	0.03
H(25B)	7.50	6.53	10.06	9.80	0.02	0.03
H(26A)	7.41	6.85	7.62	7.24	0.03	0.04
H(26B)	7.11	6.21	8.92	8.24	0.04	0.05
H(28A)	7.82	6.58	11.46	10.82	0.04	0.05
H(28B)	7.43	6.60	7.95	7.52	0.04	0.05
H(29A)	7.03	6.46	7.24	7.04	0.02	0.03
H(29B)	7.53	6.57	10.01	9.65	0.02	0.03

H(71A)	7.88	6.93	9.53	9.14	-0.07	-0.09
H(71B)	8.13	7.21	10.21	9.79	-0.07	-0.10
H(71C)	7.29	6.76	7.56	7.39	-0.06	-0.09
sum	524.80	507.51	567.47	567.09	-0.03	-0.09

Table S.2: Bond topological properties of the hydrogen bonds

D-H...A	sym./transl.	$\rho(\vec{r}_b)$	$\nabla^2 \rho(\vec{r}_b)$	D-H	H...A	d1	%	D...A	D-H...A
N(11)-H(11)...O(27)	2-x, -y, -z	0.19(2)	3.3(1)	1.0091(3)	1.8143	0.6484	35.7	2.8052(9)	167
C(2)-H(2)...N(24)	x, 1/2-y, 1/2+z	0.04(1)	0.8(1)	1.0820(3)	2.4561	0.9337	36.5	3.5175(4)	170
C(22)-H(22A)...N(1)	1-x, -1/2+y, 1/2-z	0.05(1)	0.8(1)	1.0923(3)	2.4670	0.9704	39.3	3.5409(4)	168
C(5)-H(5)...N(1)	x, 1/2-y, -1/2+z	0.05(1)	0.8(1)	1.0819(3)	2.5372	1.0303	40.6	3.4565(4)	144
C(21)-H(21A)...N(1)	x, 1/2-y, -1/2+z	0.05(1)	0.7(1)	1.0927(3)	2.6177	1.0930	41.8	3.5228(4)	141
C(25)-H(25A)...F(16)	x, 1/2-y, 1/2+z	0.05(1)	0.8(1)	1.0918(3)	2.5471	1.1557	45.4	3.2498(5)	124
C(26)-H(26B)...F(16)	x, 1/2-y, 1/2+z	0.05(1)	0.8(1)	1.0923(6)	2.5819	1.1897	46.1	3.1281(6)	113
C(21)-H(21B)...F(16)		0.02(1)	0.4(1)	1.0920(3)	2.7081	1.1768	43.5		
C(14)-H(14)...N(3)	x, y, z	0.08(1)	1.1(1)	1.0820(3)	2.5347	1.4358	56.6	3.0309(4)	109

According to Abramov [37] and Espinosa et al. [32-36] the following energetic hydrogen bond quantities are defined.

Local kinetic energy:

$$G(\vec{r}_b) = \frac{3}{10} (3\pi^2)^{\frac{2}{3}} \rho^{\frac{5}{3}}(\vec{r}_b) + \frac{1}{6} \nabla^2 \rho(\vec{r}_b),$$

Local potential energy density:

$$V(\vec{r}_b) = \frac{1}{4} \nabla^2 \rho(\vec{r}_b) - 2G(\vec{r}_b),$$

Total energy density:

$$H(\vec{r}_b) = G(\vec{r}_b) + V(\vec{r}_b),$$

Binding energy:

$$E_{HB}^1 = -\frac{1}{2} V(\vec{r}_b).$$

A geometrical relation given by Espinosa et al. [32] is defined as follows:

$$E_{HB}^2 = 25300 \cdot \exp[-3.6 \cdot (H \cdots A)] kJmol^{-1}$$

Table S.3: Energies of the hydrogen bonds

D-H...A	sym./transl.	$\rho(\vec{r}_b)$	$\nabla^2 \rho(\vec{r}_b)$	λ_3	$G(\vec{r}_b)$	$V(\vec{r}_b)$	$\frac{V(\vec{r}_b)}{G(\vec{r}_b)}$	$H(\vec{r}_b)$	E_{HB}^1	E_{HB}^2
N(11)-H(11)...O(27)	2-x, -y, -z	0.19(2)	3.3(1)	5.10	79.6	-69.2	0.87	10.3	34.6	36.9
C(2)-H(2)...N(24)	x, 1/2-y, 1/2+z	0.04(1)	0.8(1)	1.05	16.0	-10.2	0.64	5.8	5.1	3.7
C(22)-H(22A)...N(1)	1-x, -1/2+y, 1/2-z	0.05(1)	0.8(1)	1.17	16.6	-11.5	0.69	5.1	5.8	3.5
C(5)-H(5)...N(1)	x, 1/2-y, -1/2+z	0.05(1)	0.8(1)	1.10	16.6	-11.5	0.69	5.1	5.8	2.7
C(21)-H(21A)...N(1)	x, 1/2-y, -1/2+z	0.05(1)	0.7(1)	0.94	14.8	-10.6	0.71	4.2	5.3	2.0
C(25)-H(25A)...F(16)	x, 1/2-y, 1/2+z	0.05(1)	0.8(1)	1.06	16.6	-11.5	0.69	5.1	5.8	2.6
C(26)-H(26B)...F(16)	x, 1/2-y, 1/2+z	0.05(1)	0.8(1)	1.03	16.6	-11.5	0.69	5.1	5.8	2.3

C(21)-H(21B)···F(16)		0.02(1)	0.4(1)	0.53	7.7	-4.6	0.59	3.2	2.3	1.5
C(14)-H(14)···N(3)	x, y, z	0.08(1)	1.1(1)	1.51	24.6	-19.3	0.78	5.3	9.6	2.8

Figure S1: Static deformation density maps in the indole fragment from a: Theoretical calculation at the B3LYP/6-31G**-niveau (MOLDEN-representation), b: Refinement of the theoretical structure factor of model compound III (n₁-set 2468) including individual κ' -refinement (step 3), c: Experimental refinement with assigned κ' -values (n₁-set 2468, step 5).

Summary

The electron density of a substituted 4-(indol-3-yl)-quinazoline was determined, using synchrotron radiation. The effect of different sets of κ and κ' to the hydrogens and particular n_I -sets for the chlorine atom were evaluated.