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Rotational Barriers in N-Benzhydrylformamides: An NMR and DFT Study

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Abstract: N-Benzhydrylformamides are pharmacologically active compounds with anticonvulsant, enzyme-inducing, antihypoxic, and other types of biological activity. The conformational behavior of benzhydrylformamides is determined to a great extent by the presence of substituents at the nitrogen atom and in the *ortho*-position(s) of the diphenylmethane moiety. Particularly, the NMR spectra of these compounds often contain two sets of signals originating from different orientations of the formyl group. With the use of the dynamic NMR method and DFT calculations, we investigated the internal rotations of aromatic and formyl fragments and estimated the corresponding rotational barriers in N-benzhydrylformamide (BHFA), N-methyl-N-benzhydrylformamide (BHFA-NMe), and in a series of *ortho*-halogen-substituted N-benzhydrylformamides. It was found that the DFT method at M06-2X/6-311+G* level of theory satisfactorily reproduces the experimental barrier $\Delta G^{\neq}_{298}$(Formyl) of the formyl group rotation in BHFA-NMe. In BHFA, BHFA-NMe, and in the *ortho*-halogen derivatives, the calculated $\Delta G^{\neq}_{298}$(Formyl) values are close to each other and lie within 20–23 kcal/mol. On the other hand, the *ortho*-substituents significantly hinder the rotation of aryl fragment with $\Delta G^{\neq}_{298}$(Aryl) values varying from 2.5 kcal/mol in BHFA to 9.8 kcal/mol in *ortho*-iodo-N-benzhydrylformamide.

Keywords: N-benzhydrylformamide derivatives; rotational barriers; dynamic NMR; DFT calculations

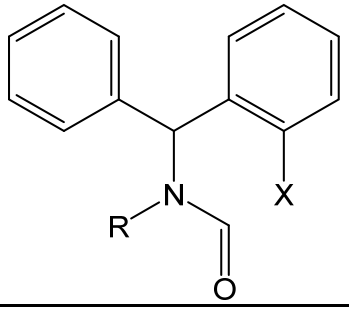
Citation: Sadvakassova, M.Z.; Khlebnikov, A.I.; Bakibaev, A.A.; Kotelnikov, O.A.; Erkassov, R.S.; Yelubay, M.A.; Issabayeva, M.A. Rotational Barriers in N-Benzhydrylformamides: An NMR and DFT Study. *Molecules* **2023**, *28*, 535. https://doi.org/10.3390/molecules28020535

Academic Editor: Carla Boga

Received: 1 November 2022
Revised: 20 December 2022
Accepted: 28 December 2022
Published: 5 January 2023

1. Introduction

The presence of a benzhydryl substituent is characteristic of many biologically active compounds. For example, benzhydrylformamides exhibit anticonvulsive [1–3], antiviral, antibacterial [4], and antihypoxic properties [5]. Other types of biological activity of benzhydrylformamides and their structural features were also investigated [5,6]. Along with characteristics of substituents, the conformational behavior of these compounds often plays a decisive role in the manifestation of biological activity, and the slightest structural changes affect the chemical properties of benzhydrylformamides [7]. In the present work, we studied the effect of substituents of the same type in the benzhydryl fragment on the conformational behavior and electronic structure of some pharmacologically active benzhydrylformamides. The objects of the study were N-benzhydrylformamide (BHFA), its *ortho*-fluoro, *ortho*-chloro-, *ortho*-bromo- and *ortho*-iodo derivatives (BHFA-oF, BHFA-oCl, BHFA-oBr and BHFA-oI, respectively), as well as N-benzhydryl-N-methylformamide (BHFA-NMe) (Scheme 1).



Compound	R	X
BHFA	H	H
BHFA-oF	H	F
BHFA-oCl	H	Cl
BHFA-oBr	H	Br
BHFA-oI	H	I
BHFA-NMe	CH_3	H

Scheme 1. Structures of the investigated N-benzhydrylformamides.

We studied the conformational equilibrium of the BHFA-NMe compound in a dimethyl sulfoxide (DMSO) solution by dynamic NMR, observing the coalescence of N-methyl group proton signals with increasing temperature, and also determined the internal rotation barriers of the compounds presented in Scheme 1 using quantum chemical calculations by the DFT method.

The choice of the studied benzhydrylformamides (Scheme 1), which were previously synthesized according to the method [7], was based on the fact that the substituents in the *ortho* position and at the nitrogen atom obviously should cause the most pronounced conformational changes compared to the parent molecule BHFA.

2. Results and Discussion

2.1. Investigation of the Internal Rotation by NMR

Using the NMR method, it is possible to determine the barrier of internal rotation in a molecule if the rate of mutual transformation of conformers (isomers) is not too high, and the nuclei exchange their chemical environment at a rate slower than the NMR time scale [8]. In this case, an increase in temperature (T) leads to a gradual convergence of distinct NMR signals of individual conformers and to their merging into one signal at a certain temperature T_c (the coalescence temperature).

Internal rotation around the C-N bond in the HC(O)-N group of formamides is quite slow due to the conjugation between the nitrogen atom and the carbonyl group [9,10]. Therefore, the signals of both conformers are observed separately in the ^{1}H NMR spectra at room temperature. Thus, in the spectrum of BHFA-NMe (Figure 1), there are two signals of methyl groups at 2.64 and 2.71 ppm. Further, the paired signals of CH methine protons at 6.23 and 6.68 ppm, as well as formyl protons at 8.28 and 8.36 ppm, are present, which are attributed to two different conformers.

With recurring registration of the ^{1}H NMR spectrum with increasing temperature, we observed that the signals of methyl protons were converged and merged into a single peak at 110 °C and higher (Figure 2).

The found coalescence temperature T_c = 110 °C (383 K) makes it possible to calculate the rotational barrier between two conformers in which the carbonyl group is in *syn*- or *anti*-orientation with respect to the benzhydryl group of the BHFA-NMe molecule (Figure 3).

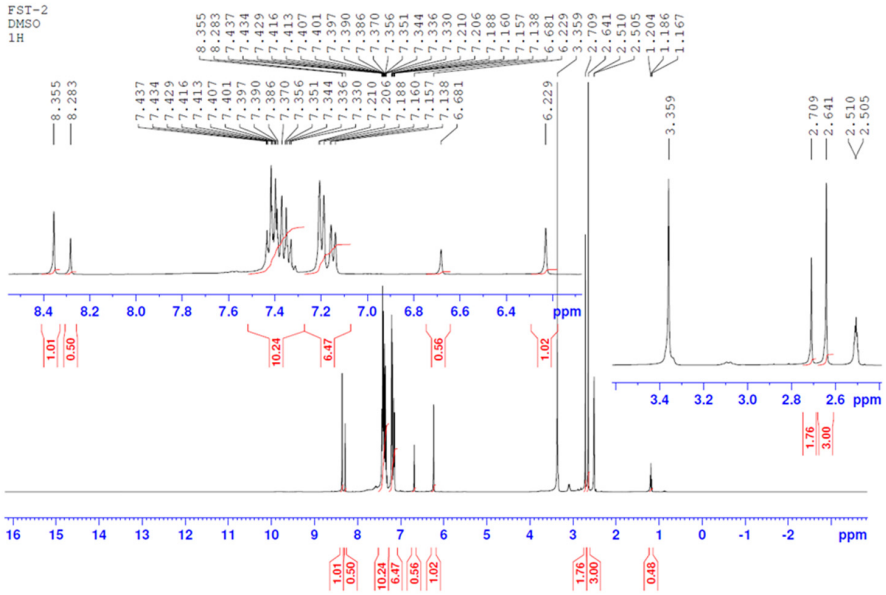
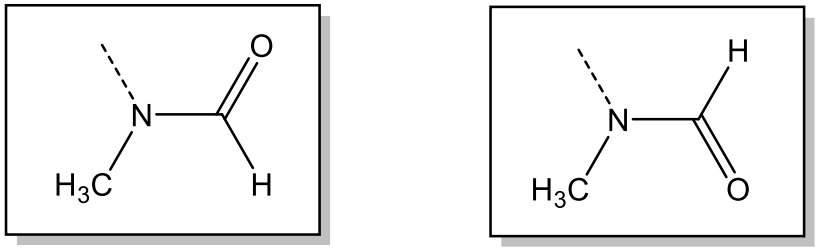


Figure 1. The ^{1}H NMR spectrum (400 MHz) of BHFA-NMe in DMSO-d_6 at 20 °C.

Figure 2. The signals of methyl protons in ^{1}H NMR spectrum of N-benzhydryl-N-methylformamide in DMSO-d_6 at temperatures of 35 (**a**), 58 (**b**), 75 (**c**), 95 (**d**), 99 (**e**), and 110 °C (**f**).



syn *anti*

Figure 3. Orientations of the formyl group in two conformers of BHFA-NMe. The chemical bond connected to the benzhydryl group is shown by the dashed line.

In addition to the value of T_c, for the calculation of the rotational barrier, it is necessary to determine the distance $\Delta\nu$ between the corresponding individual conformer signals at a low temperature [8]. From the ^{1}H NMR spectrum recorded at 20 °C (Figure 1), it can be found that the $\Delta\nu$ value for the methyl group signals equals 27.2 Hz. Calculation of the barrier $\Delta G^{\neq}$ using Equation (1) leads to a value of 19.5 kcal/mol. This value is comparable with the rotational barriers in other molecules containing a formamide fragment [9,10].

2.2. Calculation of the Internal Rotational Barriers by the DFT Method

2.2.1. Calculation of the Rotational Barriers in N-Benzhydryl-N-Methylformamide

To evaluate the possibilities of the DFT quantum chemical method to reliably evaluate the rotational barriers in substituted benzhydrylformamides, we compared the $\Delta G^{\neq}$ value obtained experimentally by the NMR method (see above) with the corresponding barrier calculated for the *syn-anti* conformational transition of the formyl moiety in compound BHFA-NMe. We applied M06-2X functional suitable for calculations of thermodynamic properties of organic compounds [11]. The used basis set 6-311+G* of triple-zeta quality contained diffuse functions and one set of polarization functions on heavy atoms to adequately account for interactions of lone electron pairs. The IEFPCM solvation model [12] was applied to evaluate the bulk effect of dimethylsulfoxide, in spite of a high polarity of the solvent. Using the explicit solvation model would be very complicated due to a variety of possible molecular ensembles formed between BHFA-NMe and dimethylsulfoxide. On the other hand, recording NMR spectra of benzhyldylformamides in less polar solvents was difficult because of low solubility.

Considering that the BHFA-NMe molecule has several internal rotational degrees of freedom and is, thus, a conformationally flexible compound, we preliminarily performed a conformational search by the molecular mechanics method using the VeraChem software. This search retrieved 66 representative conformations. Further, the first ten low-energy conformations were optimized by the DFT method. Their Gibbs energies are presented in Table S1; the corresponding Gaussian output files are archived in Supplementary Materials. The lowest-energy conformation obtained after the DFT optimization is shown in Figure 4. It has a *syn*-arrangement of the carbonyl and benzhydryl groups: the torsion angle O=C-N-CH is 0.3°. Two benzene rings are non-coplanar: the torsion angles N-CH-C_{Ar}=C_{Ar} formed by them are 80.2° and −2.0°. This conformation was used as a starting point for one-dimensional relaxed scans of the potential energy surface (PES). In one of the scans, the torsion angle corresponding to the formyl fragment rotation was varied. In the other scan, one of the phenyl groups within the benzhydryl substituent was rotated. It was found that the position of another phenyl group and the mutual rotation of the benzhydryl and formamide moieties are strongly correlated with the changes in two torsion angles mentioned above. The resulting energy profiles are shown in Figure 5.

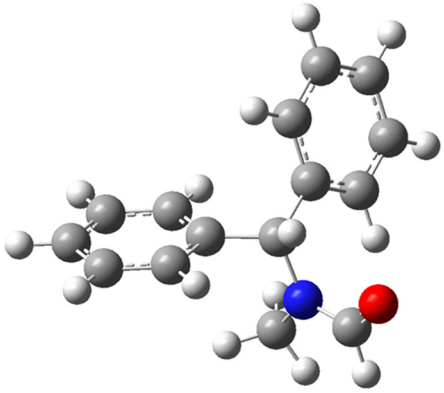
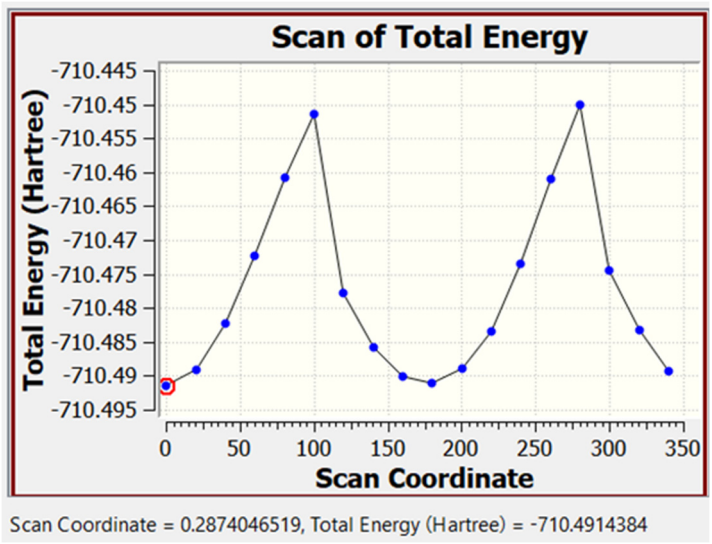
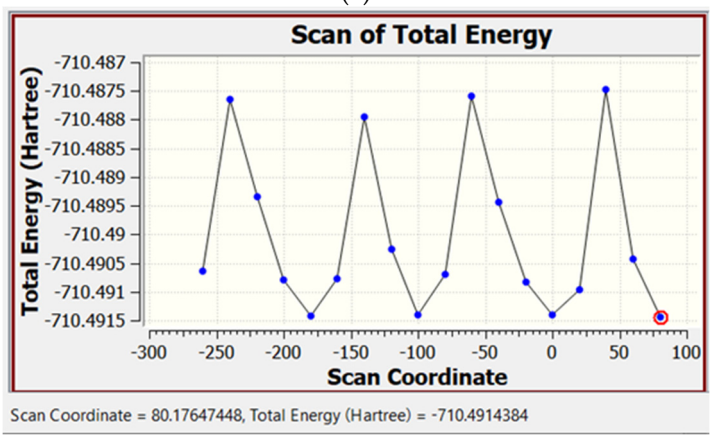


Figure 4. Conformation of BHFA-NMe molecule, which has the lowest energy according to the DFT calculation in the M06-2X/6-311+G*/IEFPCM(DMSO) approximation.



(**a**)



(**b**)

Figure 5. The energy profiles obtained by one-dimensional relaxed scanning the PES of BHFA-NMe on variation of the torsion angles O=C-N-CH (**a**) or N-CH-C_{Ar}=C_{Ar} (**b**) with a step of 20°. At each step, the remaining geometric parameters of the molecule were completely optimized in the M06-2X/6-311+G*/IEFPCM(DMSO) approximation.

With the internal rotation of the formyl group, two maxima are observed on the energy profile (Figure 5a) over the full period (360°). The curve corresponding to the

rotation of the benzene ring (Figure 5b) has four maxima approximately equal in height, which is consistent with the symmetry of the unsubstituted phenyl group. Due to the periodicity of energy profiles, a mutual transition between any two conformations (minima on the obtained curves) is possible by overcoming the energy barrier not exceeding the penultimate maximum found in the full period of internal rotation, and characteristics of this maximum should be compared with experimentally found $\Delta G^{\neq}$ value (Section 2.1). The positions of the maxima, penultimate in height on the energy profiles, were refined by searching for the corresponding saddle points of the PES, followed by an analysis of normal vibrations and the calculation of thermodynamic functions at the coalescence temperature (T_c = 383 K). Using Gibbs energies of the low-energy conformer and the transition state (saddle point), we estimated the barrier height $\Delta G^{\neq}_{383}$(Formyl) = 23.1 kcal/mol. This value satisfactorily corresponds to the barrier of 19.5 kcal/mol determined by us experimentally (Section 2.1). Some difference may be due to the effects of specific solvation not taken into account within the IEFPCM model. The calculation of thermodynamic functions by the DFT method at 298.15 K leads to the value $\Delta G^{\neq}_{298}$(Formyl) = 22.7 kcal/mol.

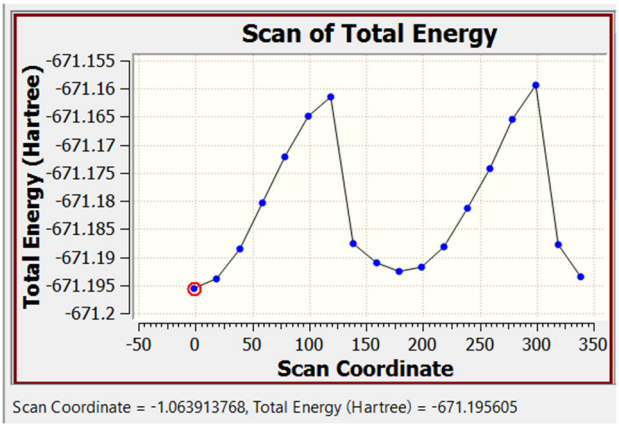
It should be noted that the conformation with *anti*-orientation of the carbonyl and benzhydryl groups, in which the torsion angle O=C-N-CH equals 180.3°, differs in Gibbs energy from the low-energy *syn* conformation by only 0.15 kcal/mol, in accordance with the presence of two substituents at the formamide nitrogen atom. This result agrees with the observation that after a long-term storage of BHFA-NMe solution in DMSO-d_6 at 20 °C, the ratio of the integral intensities of *syn*- and *anti*-methyl group singlets in the ^{1}H NMR spectrum was not changed, despite the relatively low rotational barrier. The *syn*/*anti* ratio of BHFA-NMe conformers calculated from their Gibbs energies is equal to 1.3/1 in a satisfactory agreement with relative integral intensities of the NMR signals at 2.64 and 2.72 ppm (1.7/1 at 20 °C, Figure 1).

For the rotation of phenyl group in compound BHFA-NMe, the calculated barrier $\Delta G^{\neq}_{298}$(Aryl) equals 3.06 kcal/mol.

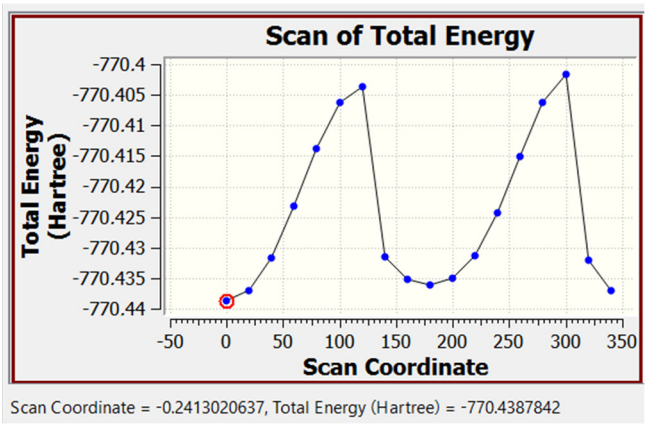
2.2.2. Calculation of Rotational Barriers in N-Benzhydrylformamide and Its *ortho*-Substituted Derivatives

The results presented above show that the DFT method can be applied to evaluate rotational barriers in benzhydrylformamides. We performed quantum chemical calculations for N-benzhydrylformamide and its derivatives containing a halogen atom in the *ortho* position of one of the benzene rings. Compounds with *ortho*-substituents in the aromatic ring are of the greatest interest in terms of studying steric interactions and their influence on the conformational behavior of molecules. The 6-311+G* basis set is not defined for bromine and iodine; hence, for these atoms, we applied LANL2DZ basis with effective core potential, which was successfully used in conjunction with Pople basis sets (see, e.g., [13]).

By analogy with compound BHFA-NMe, we performed a molecular mechanics search for conformations for BHFA, BHFA-oF, BHFA-oCl, BHFA-oBr, and BHFA-oI using the VeraChem software. For ten low-energy conformations of each compound, the geometry was optimized by the DFT method. Then, for the conformation with the lowest energy value, which, in all cases, had the *syn*-orientation of the carbonyl group and the benzhydryl fragment, one-dimensional PES scans were performed, varying the torsional angle N-CH-C_{Ar}=C_{Ar} (involving the benzene ring with an *ortho* substituent), or torsion angle O=C-N-CH. Energy profiles found on the scanning are shown in Figures 6 and 7.



(**a**)



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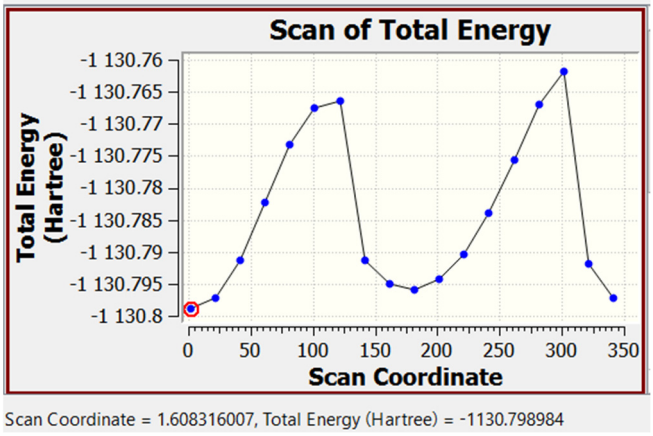

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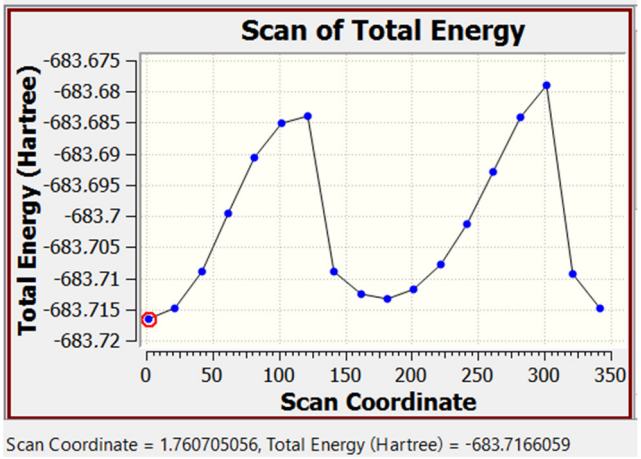

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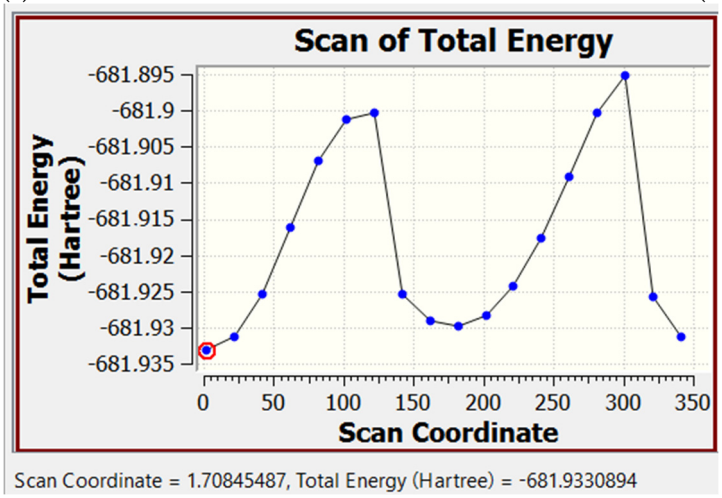

(**e**)

Figure 6. The energy profiles obtained by one-dimensional relaxed scanning the PES on variation in the torsion angle O=C-N-CH for compounds BHFA (**a**), BHFA-oF (**b**), BHFA-oCl (**c**), BHFA-oBr (**d**), and BHFA-oI (**e**) with a step of 20°. At each step, the remaining geometric parameters of the molecules were completely optimized in the M06-2X/6-311+G*/IEFPCM(DMSO) approximation.

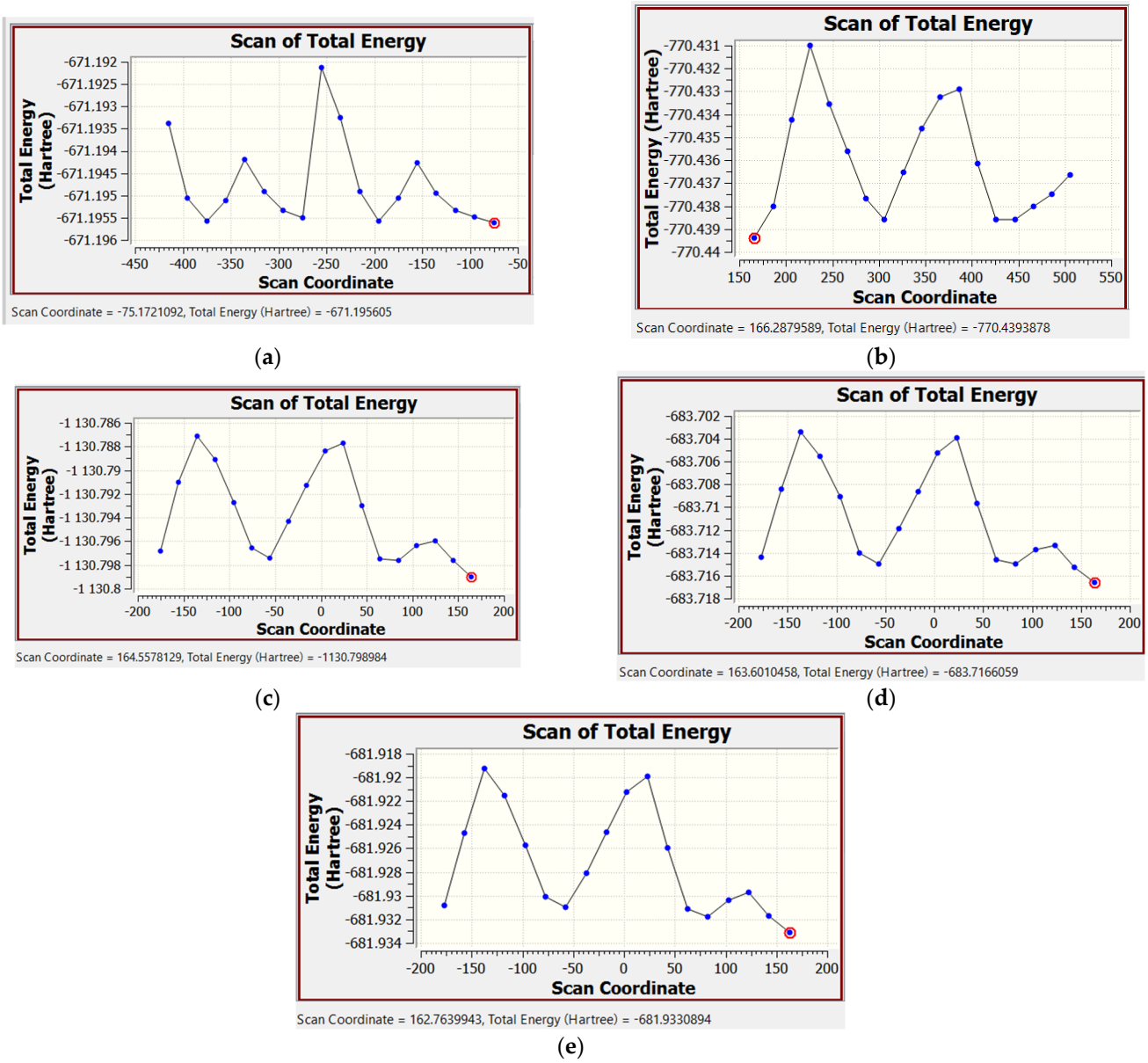

Figure 7. The energy profiles obtained by one-dimensional relaxed scanning the PES on variation in the torsion angle N-CH-C_{Ar}=C_{Ar} for BHFA (**a**), BHFA-oF (**b**), BHFA-oCl (**c**), BHFA-oBr (**d**), and BHFA-oI (**e**) found by the DFT method. At each step, the remaining geometric parameters of the molecules were completely optimized in the M06-2X/6-311+G*/IEFPCM(DMSO) approximation. For halogen derivatives, the profiles were obtained on rotation of the *ortho*-substituted benzene ring, where the largest, medium (penultimate in heght), and the lowest maxima correspond to a halogen orientation opposite to phenyl, formamide, and methine C-H fragments, respectively. Different heights of maxima in panel (**a**) can be explained by cooperative movements of formamide and two unsubstituted phenyl groups in BHFA molecule on the relaxed PES scan, unlike in BHFA-NMe containing the N-methyl substituent (Figure 5b).

On each of the obtained profiles, the maximum penultimate in height was found, for which the search for a saddle point (transition state) on the PES was performed. The thermodynamic characteristics of the lowest-energy conformers and transition states made it possible to calculate the barriers of internal rotation of the formyl and aryl groups ($\Delta G^{\neq}_{298}$(Formyl) and $\Delta G^{\neq}_{298}$(Aryl), respectively) listed in Table 1.

Table 1. The number of conformations (N_{conf}) found using the VeraChem software, the barriers ($\Delta G^{\neq}_{298}$ (Formyl) and $\Delta G^{\neq}_{298}$ (Aryl)) for the rotation of the formyl and aromatic fragments of the investigated compounds. Values of $\Delta G^{\neq}_{298}$ (*syn*→*anti*) correspond to internal rotation of the formyl group. Gibbs energies are given in kcal/mol.

Compound	N_{conf}	$\Delta G^{\neq}_{298}$(Formyl) [a]	$\Delta G^{\neq}_{298}$(Aryl) [a]	$\Delta G^{\neq}_{298}$(syn→anti)
BHFA	42	21.50	2.49	1.40
BHFA-oF	54	20.11	5.81	1.40
BHFA-oCl	42	20.42 (20.57)	8.68 (8.23)	1.61
BHFA-oBr	45	20.36 (20.62)	9.53 (8.68)	1.69
BHFA-oI	47	21.40 (21.15)	9.76 (9.19)	1.67
BHFA-NMe	66	22.65	3.06	0.15

[a] The values in parentheses were calculated in the relativistic HF ZORA approximation.

The calculated rotational barriers of the formyl group in N-benzhydrylformamide and its *o*-halogen derivatives are close to the analogous value for compound BHFA-NMe, differing from it slightly downwards, which may be due to the absence of a methyl substituent at the nitrogen atom in these molecules. On the whole, all the values of $\Delta G^{\neq}_{298}$(Formyl) found by the DFT method are very close to each other and practically independent of the presence and nature of the *ortho* substituent. As for the rotational barriers of the benzene ring with a halogen atom in the *ortho* position (or the unsubstituted phenyl group in BHFA and BHFA-NMe), they differ markedly for the compounds under study. The small-sized substituents—the *ortho*-fluorine atom or the *N*-methyl group—lead to a relatively weak increase in the value of $\Delta G^{\neq}_{298}$(Aryl) in comparison with compound BHFA (from 2.5 for BHFA to 3.1 and 5.8 kcal/mol for BHFA-NMe and BHFA-oF, respectively, Table 1), while chlorine, bromine, and iodine atoms increase the barrier to 8.7–9.8 kcal/mol. The closeness of the $\Delta G^{\neq}_{298}$(Aryl) values for BHFA-oBr and BHFA-oI is noteworthy, despite the noticeable difference in the van der Waals radii of the bromine and iodine atoms (1.95 and 2.15 Å, respectively [14]). This observation can be partially explained by differences in the electronegativity of halogens. The calculated ECP charges on F, Cl, Br, and I atoms are equal to −0.278, −0.103, −0.079, and +0.024, respectively, for the investigated *ortho*-substituted derivatives. Consequently, the iodine substituent in compound BHFA-oI has an attractive interaction with the electron-rich formamide moiety. Indeed, for the *ortho*-halogen derivatives under study, the calculated barriers $\Delta G^{\neq}_{298}$(Aryl) correspond to transition states in which the halogen atom is located near the formamide fragment. An example of such a transition state is shown in Figure 8. It should be mentioned again that it corresponds to the barrier penultimate in height on the energy profile found on scanning about the torsion angle N-CH-C_{Ar}=C_{Ar} (Figure 7e), and the transition state with the maximum energy on this profile for BHFA-oI is characterized by a barrier of 10.7 kcal/mol and corresponds to the location of the iodine atom opposite the unsubstituted phenyl group.

To evaluate the relativistic effects that can be noticeable for bromo and iodo derivatives, we reoptimized the geometries of BHFA-oI, BHFA-oBr, BHFA-oCl, and the corresponding transition states using the ZORA approach [15]. The obtained rotational barriers are presented in Table 1. The $\Delta G^{\neq}_{298}$(Aryl) values are somewhat lower in the relativistic approximation than the barriers calculated with M06-2X functional. For the investigated iodo-, bromo-, and chloro-substituted benzhydrylformamides, the differences are equal to 0.57, 0.85, and 0.45 kcal/mol, respectively. Bearing in mind that for BHFA-oCl, this methodological difference has a mainly non-relativistic origin, we can conclude that for BHFA-oBr and BHFA-oI, the influence of relativistic effects on the barrier heights is not very significant.

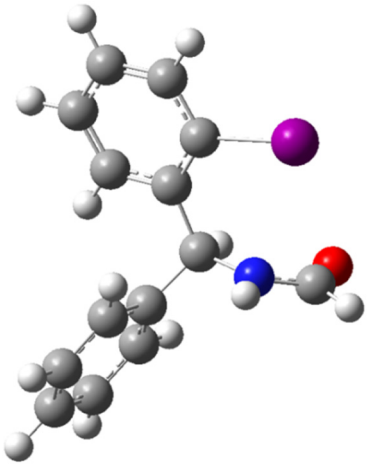

Figure 8. Structure of the transition state that occurs upon rotation of the *ortho*-substituted benzene ring in molecule BHFA-oI.

It can be seen from Table 1 that the barriers for the rotation of the aryl group are much lower than for the formyl fragment in all benzhydrylformamides studied. Hence, at room temperature, the rotation of benzene rings must be very fast compared to the relaxation time of protons. In this regard, the presence of paired signals in the ^{1}H NMR spectra is due only to slow *syn-anti* conformational transitions within the formamide group. The Gibbs energies $\Delta G^{\neq}_{298}$(*syn*→*anti*) of this transition (Table 1) obtained after optimization of the structures with *anti*-conformation taken from PES scans (Figure 6) confirm a higher stability of *syn*-conformers, which is more pronounced for BHFA and *ortho*-halogen substituted derivatives (1.4–1.7 kcal/mol). The reasons for the low value of $\Delta G^{\neq}_{298}$(*syn*→*anti*) obtained for BHFA-NMe were discussed in Section 2.2.1.

Internal rotation of the formyl group leads to a significant change in pyramidality of the nitrogen atom. According to our DFT calculations and the crystallographic data [6], the formamide moiety is fairly planar in *syn*- and *anti*-conformers, while in the corresponding transition states, the sum of valence angles at the nitrogen atom for *ortho*-halogen derivatives is about 325°; for BHFA and BHFA-NMe, this magnitude equals 328 and 335°, respectively, in agreement with earlier results on the influence of amide resonance on planarity of the nitrogen atom upon internal rotation [16–18].

3. Materials and Methods

3.1. The NMR Experiments

The ^{1}H NMR spectra of compound BHFA-NMe synthesized according to the procedure described in [7] were recorded on a BRUKER AVANCE III HD instrument with an operating frequency of 400 MHz. DMSO-d_6 was used as a solvent.

The study of coalescence of the methyl group signals was carried out by recording ^{1}H NMR spectra at temperatures of 20, 35, 52, 58, 75, 95, 99, 110, and 120 °C.

The height of the internal rotational barrier $\Delta G^{\neq}$ was determined by Equation (1) [8]:

$$\Delta G^{\neq} = RT_c[22.96 + \ln\left(\frac{T_c}{\Delta\nu}\right) \quad (1)$$

where R is the universal gas constant;

T_c—coalescence temperature, K;

$\Delta\nu$ is the difference in frequency between the methyl group NMR signals of different conformers of compound BHFA-NMe, Hz.

3.2. Quantum Chemical Calculations

The initial conformational search in the benzhydrylformamide derivatives was performed by the method of molecular mechanics with the modified Dreiding force field [19] using the VConf program of the VeraChem software package (VeraChem LLC, Germantown, MD, USA). Ten conformations of each compound with the lowest energies were further optimized by DFT (see below), and the geometric structure with the lowest energy obtained after the optimization was chosen for further calculation of rotational barriers. Quantum chemical DFT calculations were performed using Gaussian 16 program [20] on a server (16 × 2.2 GHz CPU, 16 Gb RAM) operating under Ubuntu 16.04. The M06-2X functional [11] and the 6-311+G* basis set [21,22] were used on the calculations. For bromine and iodine atoms, the LANL2DZ basis with an effective core potential [23] was applied. The bulk effect of the solvent (dimethylsulfoxide) was taken into account within the IEFPCM solvation model [12].

One-dimensional scans of the PES with varying the torsion angles O=C-N-CH or N-CH-C_{Ar}=C_{Ar} were carried out with a step of 20°. At each step, an optimization of all the other geometric parameters of the studied benzhydrylformamides was performed. To calculate a rotational barrier, we used the maximum penultimate height obtained by the scanning over the full period (360°) of each torsion angle. The barriers were calculated based on the characteristics of the corresponding transition states refined using the OPT = (TS, CALCFC, NOEIGEN) options of the Gaussian 16 program. For all the stationary points on the PES, the analysis of normal vibrations was carried out in order to establish the nature of the stationary point (a minimum or a transition state). The calculation results were visualized using GaussView 6.0 program [24].

The DFT-optimized low-energy conformers of BHFA-oCl, BHFA-oBr, BHFA-oI, and the corresponding transition states were reoptimized in the relativistic Hartree-Fock ZORA approximation [15] with ZORA-def2-SVP basis set and CPCM solvation model (dimethylsulfoxide). For clorine and bromine atoms, the triple-zeta ZORA-def2-TZVP basis was applied. For iodine atom, SARC-ZORA-TZVP basis set [25] was used. All the relativistic calculations were performed with the use of ORCA 5.0 quantum chemistry software [26].

The Gaussian and ORCA output files are available in the Supplementary Materials.

4. Conclusions

New data on the conformational behavior of biologically important benzhydrylformamides were obtained. It was found that there are significant hindrances to the free rotation of the formyl group in these molecules, which stipulate the existence of N-benzhydrylformamides as mixtures of *syn*- and *anti*-conformers at ordinary temperatures. Since the properties of these conformers, including the ability to bind to receptors and enzymes, are different, the data obtained can be valuable for predicting the interaction of benzhydrylformamide derivatives with various biotargets.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules28020535/s1, Table S1: Relative Gibbs free energies of the conformations obtained after DFT optimization of the structures initially generated by VeraChem software. ZIP-archive of Gaussian and ORCA output files obtained on the DFT and HF ZORA calculations.

Author Contributions: Conceptualization, A.I.K., A.A.B. and M.Z.S.; methodology, A.I.K. and R.S.E.; software, O.A.K.; validation, M.A.Y. and M.A.I.; formal analysis, R.S.E.; investigation, A.I.K. and O.A.K.; resources, A.A.B.; data curation, A.A.B. and M.Z.S.; writing—original draft preparation, A.I.K.; writing—review and editing, A.I.K., A.A.B. and M.Z.S.; visualization, A.I.K.; supervision, A.A.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Ministry of Science and Higher Education of the Russian Federation (project no. Nauka FSWW-2020-0011); the Tomsk Polytechnic University development program; and by the Tomsk State University Development Program (Priority2030).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in this article.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Not applicable.

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