QUANTUM-CHEMICAL STUDY OF THE STEREOCHEMISTRY OF SOME *N,N*-DIARYLAMIDES

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Abstract. Conformational distribution and rotational dynamics of two *N,N*-diarylamides, *N,N*-di(2-methylphenyl)-3',3'-dimethylbutyrylamide (**1**) and *N*-(2-methylphenyl)-*N*-(1-naphthyl)-3',3'-dimethylbutyrylamide (**2**), were modelled using the semiempirical AM1 SCF method. The results were used to predict the possible origin of the energy barriers estimated by the dynamic NMR spectroscopy.

Key words: amide, rotation, modelling.

INTRODUCTION

Conformational preferences and dynamic processes in sterically crowded amides have been the subjects of numerous studies over decades. The most common experimental tool in these investigations has been the NMR spectroscopy. However, depending on the chemical structure of the amide, the unambiguous interpretation of these spectra may be difficult due to the complicated NMR spectra arising from the more than one conformational species in the measured sample. The *N*-arylamides represent a typical example of such a situation. The relatively high rotational barriers about both the amide N–C(O) bond and nitrogen–aryl bond(s) may lead to the presence of several equilibrial atropisomers in the solution and, correspondingly, to a complicated overall NMR spectrum of the compound. The quantum-chemical modelling of the possible conformers and the potential surfaces of the respective conformational transformations may assist in clarifying the above-mentioned problems.

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QUANTUM-CHEMICAL CALCULATIONS

The quantum-chemical calculations were performed at the semiempirical level using Austin Model 1 (AM1) [1, 2] parameterization. The semiempirical approach was chosen on the basis of the size of the molecules considered in this work. Good-quality *ab initio* calculations of the potential surfaces for rotational transition barriers in the systems of this size would require very much computer time and big hardware resources. Notably, extensive quantum-chemical *ab initio* studies at various levels of theory (SCF LCAO MO, MP2–MP4, G2(MP2)) have been reported only for simple amides including formamide, *N*-methylacetamide, *N,N*-dimethylformamide, and *N,N*-dimethylacetamide [3–9]. It is well known that the AM1 method substantially underestimates the rotation barrier along the amide bond [10]; however, a good linear correlation has been found between the experimental and AM1 calculated barriers [10].

Substantial solvent effects on the amide bond rotation barriers have been reported on the basis of experimental dynamic NMR spectra measurements [11–14]. However, for large systems involving aryl substituents at the amide nitrogen atom, the calculated solvent effects have been found to be nearly constant for a series of similar molecules [15]. Therefore, only isolated molecules were studied in this work.

It has been shown that most rotational activation free energies, particularly the rotational barriers along the amide bond, are predominantly of enthalpic nature [8]. Consequently, the quantum-chemically calculated relative energies of the conformers and transition states can be used to estimate the relative populations of different conformers and the activation free energies of the rotational transformations.

Two compounds were considered in the present work: *N,N*-di(2-methyl-phenyl)-3',3'-dimethylbutyrylamide (**1**) and *N*-(2-methylphenyl)-*N*-(1-naphthyl)-3',3'-dimethylbutyrylamide (**2**):

Ar = 2-Tolyl   (**1**)

Ar = 1-Naphthyl (**2**)
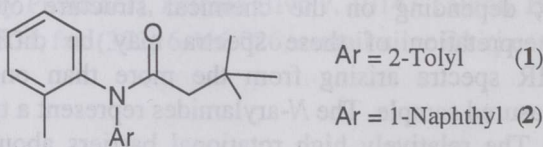
In both cases, the conformational minima and transition barriers were found by the grid search of the multidimensional potential surface contrived from all possible rotations along the N–C$_{aryl}$ bonds and along the C(O)–C(neopentyl) bond.

RESULTS AND DISCUSSION

N,N-di(2-methylphenyl)-3',3'-dimethylbutyrylamide (1)

Four conformers (**1a–1d**) were established for N,N-di(2-methylphenyl)-3',3'-dimethylbutyrylamide. The AM1 calculated heats of formation $\left(\Delta H_{f,298}^{0}\right)$, relative energies, and relative populations of different conformers at room temperature are given in Table 1.

1a   **1b**

1c   **1d**
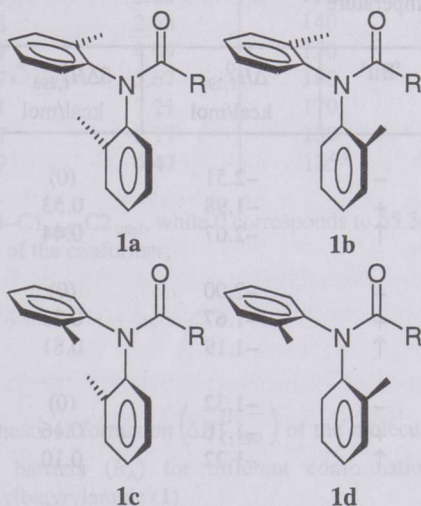
Notably, the rotation along the C(O)–C(neopentyl) bond is characterized by a low barrier. The following AM1 calculated activation energies were obtained for this rotation: $E_A = 1.05$, 0.51, 0.26, and 0.92 kcal/mol for **1a**, **1b**, **1c**, and **1d**, respectively. Consequently, the neopentyl group undergoes rapid rotation and no splitting of the methyl group signals in the NMR spectra is expected to arise from this process even at very low temperature. Therefore, the respective possible rotamers along the C(O)–C(neopentyl) bond can be assumed to correspond to a single structure. The populations p_i of different conformers arising from the rotation along the N–aryl bond were calculated according to the Boltzmann' distribution law

$$p_i = \exp(-E_i/RT)\Big/\sum_i \exp(-E_i/RT), \qquad (1)$$

where R is the universal gas constant, T is the temperature in K, and E_i denote the energies of individual conformers. Two main conformers (**1a** and **1d**) account for 74% of the population whereas the minor conformers (**1b** and **1c**) account for 26%. For convenience, only the most stable conformers related to the torsion angle between the *tert*-butyl group and the amide plane were considered

in the calculation of relative populations. However, it should be kept in mind that the precision of the quantum-chemical calculations does not exclude the conformers arising from the rotation around the C(O)–C(neopentyl) bond that must be still considered in the further discussion of the dynamic NMR spectra of this compound.

Table 1. AM1 calculated heats of formation $\left(\Delta H_{f,298}^{0}\right)$, relative energies $\left(\delta\Delta H_{f,298}^{0}\right)$, and relative populations (P) of different conformers of the N,N-di(2-methylphenyl)-3',3'-dimethylbutyrylamide (**1**) at room temperature

Conformer	'Bu[a]	$\Delta H_{f,298}^{0}$, kcal/mol	$\delta\Delta H_{f,298}^{0}$ [b], kcal/mol	P [c], %
1a	–	–2.51	(0)	48
	+	–1.98	0.53	
	↑	–2.07	0.44	
1b	–	–2.00	(0)	20
	+	–1.67	0.33	
	↑	–1.19	0.81	
1c	–	–1.32	(0)	6
	+	–1.16	0.16	
	↑	–1.22	0.10	
1d	–	–1.18	0.97	
	+	–0.62	1.53	
	↑	–2.15	(0)	26

[a] Position of the 'Bu group relative to the amide plane: + in front, – behind, and ↑ in plane (cis to the oxygen atom);
[b] relative energy to the most stable conformer with respect to the position of 'Bu group;
[c] calculated relative population of different conformers at room temperature (298 K).

All possible four rotation paths on the multidimensional molecular potential surface, each corresponding to a single $N–C_{aryl}$ bond rotation, were calculated. These correspond to the transitions **1a ⇌ 1b**, **1a ⇌ 1c**, **1b ⇌ 1d**, and **1c ⇌ 1d**. As an example, the results of the grid search of the potential surface for the transition **1b→1a** with the rotation step of 10 degrees are presented in Table 2. The AM1 SCF calculated transition energies are summarized in Table 3. Rotational barriers calculated as the difference between the transition state and the most stable conformer (i.e. **1a** from the pair **1a–1d** and **1b** from **1b–1c**) range from 7.38 kcal/mol for **1c→1a** to 8.17 kcal/mol for **1b→1d**. The similarity of these barriers suggests that only one coalescence process, corresponding to the

Table 2. AM1 calculated heats of formation $\left(\Delta H_{f,298}^0\right)$ and relative energies $\left(\delta\Delta H_{f,298}^0\right)$ for the points at the potential surface corresponding to the conformational change **1b→1a**

Relative angle[a]	$\Delta H_{f,298}^0$, kcal/mol	$\delta\Delta H_{f,298}^0$,[b] kcal/mol	Relative angle[a]	$\Delta H_{f,298}^0$, kcal/mol	$\delta\Delta H_{f,298}^0$,[b] kcal/mol
(0)[c]	−2.00	(0)	100	1.26	3.26
10	−1.62	0.38	110	0.42	2.42
20	−1.15	0.85	120	−0.12	1.88
30	1.00	3.00	130	−0.35	1.65
40	0.68	2.68	140	−0.49	1.51
50	2.09	4.09	150	−1.40	0.60
60	3.67	5.67	160	−1.94	0.06
70	5.21	7.21	170	−2.22	−0.22
80[d]	6.17	8.17	180	−2.40	−0.40
90	2.47	4.47	185[e]	−2.51	−0.51

[a] Dihedral angle $\angle$ C(O)–N–C1$_{tolyl}$–C2$_{tolyl}$, while 0 corresponds to 65.36°;
[b] calculated relative energy of the conformer;
[c] conformer **1b**;
[d] transition state;
[e] conformer **1a**.

Table 3. AM1 calculated heats of formation $\left(\Delta H_{f,298}^0\right)$ of the molecule in the transition state and the respective rotational barriers (E_A) for different conformational changes of N,N-di(2-methylphenyl)-3',3'-dimethylbutyrylamide (**1**)

Rotation	$\Delta H_{f,298}^0$, kcal/mol	E_A
1a→1b	5.64	8.15
1a→1c	5.55	8.06
1b→1a	6.17	8.17
1b→1d	6.17	8.17
1c→1a	5.38	7.38
1c→1d	5.73	7.73

equilibration of the isomers with the tolyl methyl groups on the one side of the amide plane (**1a** and **1d**) and the isomers with the methyls on different sides of the amide plane (**1b** and **1c**), should be observable in the dynamic NMR spectra of this compound. The calculated activation energies also indicate that the rate of the conformational transition **1a** (**1d**) to **1b** (**1c**) is somewhat slower than that of the reverse process. A closer study of the structure of rotational transition states along the N–C$_{aryl}$ bonds, however, reveals that the NC$_{tolyl1}$C$_{tolyl2}$ plane has been turned nearly orthogonal to the plane defined by the carbonyl group, with the nitrogen atom diverted essentially pyramidal. In other words, these transition

states correspond simultaneously to the transition state of the rotation along the amide bond. As mentioned above, the AM1 method underestimates significantly the rotational barriers of these bonds. Still, a satisfactory correlation has been found between the AM1 calculated transition barriers and experimentally measured activation energies for a series of amides, thioamides, ureas, and thioureas. Using the corresponding linear relationship [10]

$$\Delta G^{\neq}_{liquid} = 1.6 E_A (AM1) + 4.5 \quad kcal/mol \tag{2}$$

the barrier for the most probable rotational transition ($\mathbf{1a} \rightleftharpoons \mathbf{1c}$) is estimated as 17.40 kcal/mol for $\mathbf{1c} \rightarrow \mathbf{1a}$ and 16.31 kcal/mol for the reverse process, in excellent accordance with the experimentally measured value $\Delta G^{\neq}_{liquid} =$ 17.27 kcal/mol [J. Lill & G.-P. Schiemenz, pers. comm.] (for comparison, in less crowded N-isopropyl-N-(2-tolyl)formamide-Z, the respective rotational barrier about the N–C_{aryl} bond $\Delta G^{\neq}_{liquid}$ = 16.2 kcal/mol has been determined at the coalescence temperature [J. Leis, pers. comm.].) As mentioned above, this rotational barrier corresponds also to the transition state for the amide bond rotation and therefore both methyls of the tolyl groups become equivalent at the coalescence temperature.

However, an experimentally observed further splitting of the NMR spectra of the methyl groups as well as the methylene hydrogens of the neopentyl group at low temperatures indicates the presence of another conformational separation (with an experimental $\Delta G^{\neq}_{liquid}$ = 13.19 kcal/mol) [J. Lill & G.-P. Schiemenz, pers. comm.]. This can be assigned to the concerted hindered rotation of tolyl groups, corresponding to the transformation of the conformers $\mathbf{1a}$ to $\mathbf{1d}$ and $\mathbf{1b}$ to $\mathbf{1c}$, respectively. The respective AM1 calculated transition barriers are $E_A(AM1)$ = 6.79 and 6.44 kcal/mol. However, the AM1 calculated barrier for the interconversion between the cisoidal and transoidal forms with respect to the relative position between the planes defined by the tolyl group and the amide group of each of these conformers is about 2.5 kcal/mol. That is much less than the barrier for the $\mathbf{1a} \rightarrow \mathbf{1d}$ and $\mathbf{1b} \rightarrow \mathbf{1c}$ interconversions and, therefore, those pairs can be essentially considered as enantiomers. Also in this case, the calculated structure of the transition states is similar to those for the amide bond rotation. The predicted (according to Eq. (2) for the amide bond rotation) $\Delta G^{\neq}_{liquid}$ = 15.36 and 14.80 kcal/mol for the two enantiomerization processes ($\mathbf{1a} \rightarrow \mathbf{1d}$; $\mathbf{1b} \rightarrow \mathbf{1c}$) are somewhat higher than the experimentally observed rotational barrier for this compound (13.19 kcal/mol [J. Lill & G.-P. Schiemenz, pers. comm.]). However, the latter value, estimated from the coalescence temperature of the dynamic NMR spectra, represents obviously the average of two rotational barriers ($\mathbf{1a} \rightarrow \mathbf{1d}$; $\mathbf{1b} \rightarrow \mathbf{1c}$) and would be underestimated due to the chemical exchange between $\mathbf{1a}$ and $\mathbf{1c}$.

N-(2-methylphenyl)-N-(1-naphthyl)-3',3'-dimethylbutyrylamide (2)

The conformational space of this compound is more complicated because one of the N-substituents (e.g., the naphthyl group) can be either in the *cis*- or *trans*-position to the carbonyl oxygen of the amide group. The corresponding structures will be referred in the further discussion as the E and Z conformations.

2b (E)   2f (Z)
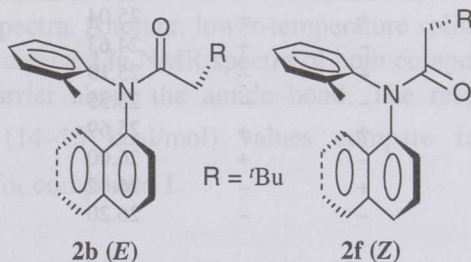
Similarly to compound **1**, it was found that the rotation of the *tert*-butyl group along the C(O)–C(neopentyl) bond is characterized by a very low barrier (<1 kcal/mol). Therefore, only the conformers corresponding to the lowest minimum for this rotation (altogether eight different conformers) will be considered in the further discussion. The definition of the conformers, their AM1 calculated heats of formation $\left(\Delta H_{f,298}^{0}\right)$, relative energies $\left(\delta\Delta H_{f,298}^{0}\right)$, and populations are given in Table 4. The Z conformers seem to be preferred (by about 1 kcal/mol) over the E conformers. However, within the precision of the theoretical method applied (AM1) this is not significant. Moreover, it has been noticed that the E/Z conformational preference may be substantially shifted by solvents [9, 16]. The calculated transition barriers between different conformers are given in Table 5. Importantly, in most cases (except of transformation **2e→2g**), the rotation along the N–C$_{aryl}$ bond leads to the concerted rotation along the amide bond with the respective interchange between the Z and E conformations. Therefore, the exchange between the conformers **2a→2g**, **2c→2g**, or **2c→2f** will lead to the equalization of different positions of the methyl at the tolyl group and of the methylene hydrogens at the neopentyl group. The predicted free energy of activation for these transitions (according to Eq. (2)) ranges from $\Delta G_{liquid}^{\neq} = 17.75$ kcal/mol to $\Delta G_{liquid}^{\neq} = 18.45$ kcal/mol.

A lower energy transition state between two twisted conformers **2b→2c** was also found for this compound. The respective AM1 calculated $E_A = 6.35$ kcal/mol corresponds to the theoretically predicted $\Delta G_{liquid}^{\neq} = 14.66$ kcal/mol in the solution. The smaller value as compared to the respective barrier of compound **1** agrees with the observation that the amide bond rotational barrier decreases at a more crowded nitrogen atom [17].

Table 4. AM1 calculated heats of formation $\left(\Delta H_{f,298}^0\right)$, the relative energies $\left(\delta\Delta H_{f,298}^0\right)$ of the conformers of N-(2-methylphenyl)-N-(1-naphthyl)-3',3'-dimethylbutyrylamide (**2**), and their relative populations (P)

Conformer	E-Z^a	T^b	N^c	$\Delta H_{f,298}^0$, kcal/mol	$\delta\Delta H_{f,298}^0{}^d$, kcal/mol	P^e, %
2a	Z	+	+	25.04	0.41	20
2b	Z	–	+	24.63	(0)	40
2c	Z	+	–	25.19	0.56	16
2d	Z	–	–	25.55	0.92	9
2e	Z	+	+	25.69	1.05	7
2f	Z	–	+	26.00	1.47	3
2g	Z	+	–	26.02	1.49	3
2h	Z	–	–	26.20	1.67	2

^a E or Z conformation considering the position of the naphthyl group with respect of the amide oxygen;
^b relative position of the tolyl group (+, turned to the same side of the amide plane as the neopentyl group; –, turned to the opposite side);
^c relative position of the naphthyl group (+, turned to the same side of the amide plane as the neopentyl group; –, turned to the opposite side);
^d relative energy to the most stable conformer (**2b**);
^e calculated relative population of different conformers at room temperature (298 K).

Table 5. AM1 calculated activation barriers (E_A) for different conformational transitions of N-(2-methylphenyl)-N-(1-naphthyl)-3',3'-dimethylbutyrylamide (**2**)

Rotation	E_A, kcal/mol	Rotation	E_A, kcal/mol
2a→2f	11.30	2c→2f	8.60
2a→2g	8.72	2d→2g	9.42
2b→2e	16.41	2d→2h	7.17
2b→2f	11.60	2e→2g	8.48
2c→2g	8.28		

CONCLUSIONS

The dynamic NMR spectra of N,N-diaryl-3',3'-dimethylbutyrylamides can be quantitatively interpreted on the basis of the semiempirical quantum-chemical AM1 SCF investigation of the full conformational potential surface of these compounds. Notably, it has been found that the rotational transition states about the N–C$_{aryl}$ bonds coincide with the transition states of the rotation around the amide (N–C(O)) bond, with the plane defined by the amide nitrogen atom and two aryl carbon atoms connected to it turned almost perpendicular to the NCO

plane and nitrogen atom itself substantially pyramidalized. In the case of N-(2-methylphenyl)-N-(1-naphthyl)-3',3'-dimethylbutyrylamide (**2**), the rotation along the N–C$_{aryl}$ bond forces also a concerted rotation along the amide bond, leading to the interchange between the E and Z conformations at this bond. In the case of compound **1**, the AM1 estimated $\Delta G^{\neq}_{liquid}$ (17–18 kcal/mol) for the respective conformational transition is in an excellent agreement with the corresponding experimental value, calculated at the coalescence temperature of the dynamic NMR spectra. Another, lower-temperature splitting of the signals of isotopic groups was detected in NMR spectra of both compounds, corresponding to the rotational barrier about the amide bond. The respective theoretically predicted $\Delta G^{\neq}_{liquid}$ (14–15 kcal/mol) values compare favourably with the experimental value for compound **1**.

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MÕNEDE N,N-DIARÜÜLAMIIDIDE STEREOKEEMIA KVANTKEEMILISED UURINGUD

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On rakendatud poolempiirilist kvantkeemilist AM1 SCF meetodit ja näidatud, et N,N-diarüül-3',3'-dimetüülbutürüülamiidide dünaamilisi TMR spektreid võib nii kvalitatiivselt kui ka kvantitatiivselt interpreteerida nende ühendite potentsiaalipindade modelleerimise kaudu. Täpsemalt on käsitletud N,N-di (2-metüülfenüül)- (1) ja N-(2-metüülfenüül)-N-(1-naftüül)-3',3'-dimetüülbutürüülamiidi (2). Arvutatud konformatsiooniliste üleminekute potentsiaali pindade põhjal on ennustatud reaalselt võimalike ja TMR spektrites kajastuvate dünaamiliste protsesside parameetrid. Samuti on leitud, et kvantkeemiliselt (AM1 SCF) arvutatud rotatsioonibarjäärid on heas korrelatsioonis eksperimentaalsete aktivatsiooni vabaenergiatega.