C–N bond rotation and E–Z isomerism in some N-benzyl-N-methylcarbamoyl chlorides: A DFT study

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Abstract

The current report presents the first theoretical study of the restricted C–N bond rotation in carbamoyl chlorides. Several N-benzyl-N-methylcarbamoyl chlorides were investigated, with varying pattern of substitution in the aromatic ring. Optimizations and frequency calculations were conducted employing DFT at the B3LYP/6-31+G(d) level of theory. Each of the studied structures exhibits a pair of rotamers (s-Z and s-E), generated upon rotation around the C(=O)–N bond. The s-E isomer is the global minimum in every case, but the preference for it is usually less than 1 kcal/mol. Two possible transition state structures were identified for the rotamer interconversion: TS_{syn} and TS_{anti}, in close analogy to other related compounds, such as amides and carbamates. In contrast to the two latter types, however, the preferred transition state in the case of carbamoyl chlorides is TS_{syn}, which we attribute to a stabilizing gauche effect. The optimized minima structures of the studied carbamoyl chlorides were subjected to GIAO B3LYP/6-311+G(2d,p) calculations, and the resultant isotropic shifts were found to be in excellent agreement with available experimental values. This has allowed us to provide unambiguous NMR signal assignments for the s-E and s-Z isomers of the studied compounds.

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Keywords: C–N bond rotation; Restricted rotation; Rotamers; Carbamoyl chloride; DFT; Gauche effect; GIAO; NMR; Chemical shifts

1. Introduction

The hindered rotation around an amide C–N bond is one of the well-known and carefully studied phenomena in organic chemistry [1–3]. The partial double bond character of the C–N bond arises through conjugation of the lone pair at the N-center with the carbonyl moiety. This leads to planarity at the amide nitrogen center and an unusually high, for a formal single bond, rotation barrier, which causes the generation of distinct s-E and s-Z isomers, often detectable through their separate sets of signals in NMR spectra. Similar features have been observed in other, related structures, such as carbamates [4–8] and ureas [9–12], which have also become subject of considerable interest. Carbamoyl chlorides, on the other hand, have received less attention [13–16], even though they are common precursors in the preparation of both carbamates and ureas. Their NMR spectra have been found to exhibit the typical patterns, associated with the restricted C–N bond rotation [13,16]. However, as a class of compounds, they have not been the subject of any theoretical studies, with the single exception of dimethylcarbamoyl chloride, whose optimized structure and GIAO NMR data were reported by Jackowski and Leš [15].

In our recent efforts to synthesize some substituted N-benzyl-N-methylocarbamates and ureas, we had to prepare the corresponding carbamoyl chlorides as precursors,
and were challenged to provide NMR spectral assignments for the s-E and s-Z isomer in each case. Hence we undertook a theoretical study on a class of structures \(1a\)–\(h\), in order to achieve the following:

(1) Optimize the rotamers (s-E and s-Z) arising through rotation around the C(=O)–N bond and calculate the corresponding gas-phase equilibrium constants.

(2) Identify and optimize the transition state structure(s) connecting the s-Z and s-E rotamers. Calculate the rotation barriers and compare them with available data for related structures (carbamates, amides, ureas).

(3) Conduct NMR calculations and compare the resultant theoretical shift values with available experimental data to provide signal assignments for the s-E and s-Z isomers.

2. Results and discussion

2.1. Computational protocol

All calculations were performed using the Gaussian03/ GaussView software package [17] on a Linux-operated QuantumCube QS4-2400C by Parallel Quantum Solutions [18], or the Gaussian03W/GaussViewW package on a PC. Calculations were conducted at 298 K, using DFT at the B3LYP/6-31+G(\(d\)) level [19–21]. B3LYP calculations have been conducted in several recent studies on related structures, such as carbamates and amides [3,5–7], which, in the interest of more direct comparison, determined the choice of functional, regardless of the fact that Gaussian03 has other functionals, such as MPW1k or BB1k, that are more specifically implemented for thermochemical kinetics. All minima and transition state structures were validated by subsequent frequency calculations at the same level of theory. The minimum structures had sets of only positive second derivatives, while transition states all had one imaginary frequency. Transition state searches were conducted employing the Transit-Guided Quasi-Newton method (STQN, opt = qst2 or qst3), or the Berny algorithm (opt = TS) [22,23]. Values of free energy changes were obtained after frequency calculations and zero-point energy corrections. Scaling factors for the ZPE values are available for related levels of theory, such as B3LYP/6-31+G(\(d\)) and B3LYP/6-31G(2\(d\),2\(p\)), and are 0.9806 and 0.983 correspondingly, i.e. very close to unity. In addition, it was found that the s-E and s-Z isomer for each studied structure (as well as the TS$_{syn}$ and TS$_{anti}$ structures) had very close or identical ZPE values (see Table S1, Supporting Information). Introduction of the same small correction, due to the scaling factor, did not change the values of \(\Delta G\) or \(\Delta G^*\) at all. Based on this, we considered scaling ZPE values unnecessary.

NMR calculations were performed using the GIAO method as incorporated in the Gaussian03 software pack-

age [24–27]. NMR shifts were computed at the B3LYP/6-31+G(2\(d\),2\(p\)) level of theory, on the B3LYP/6-31+G(\(d\)) optimized structures. GIAO B3LYP calculations have been reported in more than 200 articles during the past 10 years and the use of the B3LYP/6-31+G(2\(d\),2\(p\)) functional/basis set is generally recommended as a computationally inexpensive, yet accurate means for prediction of chemical shifts. Values for the \(^1\)H and \(^{13}\)C isotropic chemical shifts were referenced to the corresponding values for TMS, calculated at the same level of theory.

2.2. Restricted rotation around the C–N bond: s-E and s-Z isomers, free energy barriers and rates of interconversion

The conjugation of the nitrogen lone pair and generation of a partial C–N double bond leads to the appearance of s-E and s-Z isomers for each of the studied carbamoyl chlorides, as shown in Fig. 1. Calculations demonstrate that for each of the studied structures the s-E and s-Z isomer are virtually isoenergetic, with less than 1 kcal/mol preference for the s-E rotamer, with the exception of \(1c\) and \(1g\) (Table 1). The Gibbs free energy difference does not show any clear dependence on the nature of the substituent. Although generally electron-donating groups (\(1e\), \(1f\), \(1b\)) seem to lead to a lower thermodynamic difference, while electron acceptors (\(1c\), \(1g\)) increase the free energy gap, there are discrepancies in that trend, notably \(1h\). An experimental value for \(\Delta G\) for compound \(1a\) is available, based on previous NMR studies, and it compares very well with the theoretical result. The equilibrium constants \(K_{Z,E}\) and the corresponding ratios s-Z:s-E are also shown in Table 1.

Images of the stationary points for structure \(1a\) are shown in Fig. 2, while selected structural data for the stationary points of all structures \(1a\)–\(h\) are listed in Table 2. It is evident from the data in Table 2 that the optimized minima for each chloride exhibit near planarity of the car-

![Fig. 1. s-E/s-Z isomerization of structures 1a–h through restricted rotation around the C(=O)–N bond.](image-url)
Table 1
Calculated thermodynamic and kinetic parameters for the restricted C–N bond rotation in carbamoyl chlorides 1a–h

<table>
<thead>
<tr>
<th>Chloride</th>
<th>$\Delta G_{298}$ [kcal/mol]</th>
<th>$K_{Z,E}$</th>
<th>s-Z/s-E</th>
<th>$\Delta G_{syn}^a$ [kcal/mol]</th>
<th>$\Delta G_{anti}^a$ [kcal/mol]</th>
<th>$\Delta G_{syn/anti}^a$ [kcal/mol]</th>
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<tr>
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<td>-0.4 (-0.2)</td>
<td>1.97</td>
<td>34:66</td>
<td>16.2 (17.1)</td>
<td>18.1</td>
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<tr>
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<td>2.78</td>
<td>26:74</td>
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All values from B3LYP/6-31+G(d) calculations.

$^a$ Values for the s-Z to s-E conversion.

$^b$ Italicized values in parentheses based on NMR studies, from Ref. [13].

bamoyl fragment, especially the corresponding s-E isomer, for which the values of the relevant dihedral angles (see Table 2) do not exceed 2°. The s-Z isomers show a slightly greater pyramidalization at the N-center.

The structures of the transition states, on the other hand, clearly demonstrate the diminished interaction of the nitrogen lone pair with the carbonyl moiety. The C–N bond is considerably elongated, by an average of 0.06 Å, and a much greater degree of pyramidalization is observed at the nitrogen center (between about 27° for the TS$_{syn}$ structures and 32° for the TS$_{anti}$). As with other, related structures (amides, car bamates), the interconversion of rotamers can take place through one of two different transition states: TS$_{syn}$ and TS$_{anti}$ (Fig. 1). In one of them (TS$_{syn}$) the lone pair of the pyramidalized N-center points in direction of the carbonyl oxygen (i.e. syn to the O-center), while in the other it is anti to the carbonyl oxygen (TS$_{anti}$). Theoretical studies of amides and carbamates have revealed that in most cases the TS$_{anti}$ is the preferred transition state, at least in the gas phase. Wiberg et al. performed a series of $G_2$(MP2)/6-31+G(d,p) calculations and determined that TS$_{anti}$ is favored by 2.5 kcal/mol for dimethylacetamide (DMA) [3], but the same study indicated a 0.4 kcal/mol preference for TS$_{syn}$ in the case of dimethylformamide (DMF), identical with the more recent, DFT-based result of Basso and Pontes [6]. For carbamates the available data support a slight preference for the TS$_{anti}$ structure. Thus, Rablen reported a 0.8 kcal/mol preference for TS$_{anti}$ for methyl N,N-dimethylcarbamate (at the MP2/6-311++G(d,p)//MP2/6-31+G(d) level) [5], while cyclohexyl N,N-dimethylcarbamate was reported to have a 0.5–0.8 kcal/mol preference for TS$_{anti}$ depending on the configuration of the cyclohexyl–O bond [6].

The results in Table 1 demonstrate that there is a clear preference for the TS$_{syn}$ structure in all of the studied carbamoyl chlorides, by about 2 kcal/mol. We attribute this interesting difference between carbamoyl chlorides on one hand, and amides and carbamates on the other to the presence of chlorine in the former structures. While in both TS$_{syn}$ and TS$_{anti}$ the nitrogen lone pair is unfavorably aligned with the dipole of either the C=O or the C=Cl bond, it seems overall advantageous to have it anti to the C=Cl bond (and therefore syn to the C=O bond), this being the necessary arrangement for a stabilizing gauche effect. The latter would involve transfer of some electron density from the carbamoyl nitrogen and the carbonyl oxygen lone pairs to the $\sigma^*$ orbital of the C=Cl bond, as represented schematically in Fig. 3. The effect would lead to an increased C–Cl distance, while the C(=O)–N and C=O distances would be diminished. These expectations are supported by the variations in bond lengths reported in Table 2. Thus the C–Cl bond for all TS$_{syn}$ structures is in the range 1.85–1.86 Å. It is 0.03–0.04 Å longer than its value in the s-Z and s-E rotamers and the difference is even greater (0.05–0.06 Å) when compared to the result for TS$_{anti}$. The C(=O)–N bond is consistently shorter in TS$_{syn}$ compared to TS$_{anti}$ and the same trend is observed for the C=O bond.

There are very few available experimental values on the thermodynamics and kinetics of the s-E/s-Z isomerization process in carbamoyl chlorides. Proton NMR studies of...
for some fluorinated -arylcarbamoyl chlorides [14]. The
McArthur et al. on a series of -alkyl- -benzylcarbamoyl
chlorides (variation of the alkyl group) revealed Gibbs free
energy of activation for the s-Z/s-E interconversion
in the range of 16.5–17.1 kcal/mol (studies in CDCl 3) [13].
In particular, a value of 17.1 kcal/mol was determined for
structure 1a, which is 1 kcal/mol higher than the theoretical
result reported in this work, but small differences can be
accounted for on the basis of solvent effects. Gerig and
co-workers, using fluorine NMR, derived the parameters
for some fluorinated -arylcarbamoyl chlorides [14]. The
Gibbs free energy of activation was determined in the range
of 14.6–14.8 kcal/mol for both N,N-bis(4-fluorophenyl)
carbamoyl chloride and N-phenyl-N-(4-fluorophenyl)carbamoyl chloride, while the value for N,N-bis(2-fluorophenyl)carbamoyl chloride was estimated at 17.4 kcal/mol.

How do the calculated activation barriers for carbamoyl
chlorides relate to the computed/experimental gas phase
tables of other, similar structures? Barriers for amides are
higher or comparable. Thus, reported calculated barri-
ers for DMF range from 19.4 kcal/mol (Ref. [3],
G2(MP2)//MP2/6-31+G(d,p) calculation) to 21.0 kcal/mol
(Ref. [6], B3LYP/6-311+G(d,p) calculation), with an
experimental gas phase value of 19.3 kcal/mol [3,28]. How-
ever, the barrier for dimethylacetamide is considerably
lower. A value of 15.6 kcal/mol was calculated [3], and is very
close to the experimental gas phase value of 15.3 kcal/mol
[3,5,29]. Values for carbamates are generally lower. Effective
computed barriers of 12.8 and 14.9 kcal/mol were reported
for methyl -dimethylcarbamate and cyclohexyl N,N-
dimethylcarbamate correspondingly [5,6]. DFT calculations
on three tert-butyl N-methylcarbamates, with an N-phenyl,
N-2-pyridyl and N-2-pyrimidyl substituent correspondingly,

\[ \text{Fig. 3. Stabilizing gauche effect in TS}_{\text{syn}}, \text{arising from orbital interaction} \]

\[ \text{of the lone pairs at the carbamoyl nitrogen and the carbonyl oxygen} \]

\[ \text{centers with the } \sigma^* \text{ orbital of the C–Cl bond.} \]

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<th>N–C(=O)</th>
<th>Cl–C(=O)</th>
<th>C≡O</th>
<th>Cl–C(=O)–N–C(H3)</th>
<th>C≡O–C(H3)–C(H2)–N</th>
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Results form B3LYP/6-31+G(d) calculations. Bond lengths in angstroms [Å]. Dihedral angles in degrees.
led to barriers of 13.4, 10.2 and 5.7 kcal/mol [7]. Still lower are the reported values for ureas. Thus, HF/6-31G(d) calculations on tetram-ethylurea led to a barrier value of 8.9 kcal/mol[11]. The reported values for urea range from 7.0 kcal/mol (DFT study) to 8.1 kcal/mol (at the MP2/6-31G(d) level) [12].

Higher values for carbamoyl chlorides, compared to carbamates and ureas, are to be expected. In the case of carbamates and ureas the oxygen, or second nitrogen center, respectively, provides significant electronic perturbation, which leads to decreased demand for C(O)A conjugation, and, consequently, to a lower rotation barrier. In carbamoyl chlorides similar participation by the chlorine center would be minimal, because of orbital mismatch. It is therefore to be expected that the conjugation of the nitrogen lone pair and the barrier to rotation would be greater in carbamoyl chlorides. The significant difference (~2 kcal/mol) between ΔG°syn and ΔG°ant has been identified for the s-Z/s-E interconversion. For all of the studied carbamoyl chlorides the TS_{syn} structure is thermodynamically favored, by about 2 kcal/mol. This is in contrast to the general preference for the TS_{anti} in the cases of amides and carbamates. We have attributed the difference to a unique stabilizing gauche effect in the TS_{syn} structure of carbamoyl chlorides. We have also conducted GIAO NMR calculations, which have provided chemical shift values that are in excellent agreement with the experimental data. They have been used for definitive signal assignments to the corresponding rotamers.

3. Conclusions

This article has described the first theoretical study on the restricted C(=O)—N bond rotation process in carbamoyl chlorides. Our results, based on gas-phase calculations, indicate that for each of the studied structures the s-E and s-Z isomer are almost isoenergetic, with a calculated small preference (typically less than 1 kcal/mol) for the s-E structure. Two distinct transition states, TS_{syn} and TS_{anti}, have been identified for the s-Z/s-E interconversion. For all of the studied carbamoyl chlorides the TS_{syn} structure is thermodynamically favored, by about 2 kcal/mol. This is in contrast to the general preference for the TS_{anti} in the cases of amides and carbamates. We have attributed the difference to a unique stabilizing gauche effect in the TS_{syn} structure of carbamoyl chlorides. We have also conducted GIAO NMR calculations, which have provided chemical shift values that are in excellent agreement with the experimental data. They have been used for definitive signal assignments to the corresponding rotamers.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.theochem.2007.10.028.

References

[18] Parallel Quantum Solutions, 2013 Green Acres Road, Suite A, Fayetteville, Arkansas 72703.