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C – N Bond Rotation and E – Z Isomerism in Some N-Benzyl-N-Methylcarbamoyl Chlorides: A DFT Study

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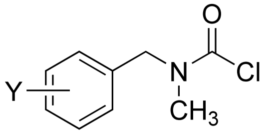
Abstract

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.

Keywords: C – N bond rotation, restricted rotation, rotamers, carbamoyl chloride, DFT, gauche effect, GIAO, NMR, chemical shifts

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 Leś.[15]



1a: Y = H, **1b:** Y = 4-CH_3,
1c: Y = 4-NO_2, **1d:** Y = 3-NO_2,
1e: Y = 4-OCH_3, **1f:** Y = 3-OCH_3,
1g: Y = 4-CF_3, **1h:** Y = 4-pyridyl

In our recent efforts to synthesize some substituted N-benzyl-N-methylcarbamates 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.

Results and Discussion

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/6-31G(d)* and *B3LYP/6-31G(2df,2p),* 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 ΔG or $\Delta G^{\neq}$ 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 package.[24-27] NMR shifts were computed at the *B3LYP/6-311+G(2d,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/6-311+G(2d,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.

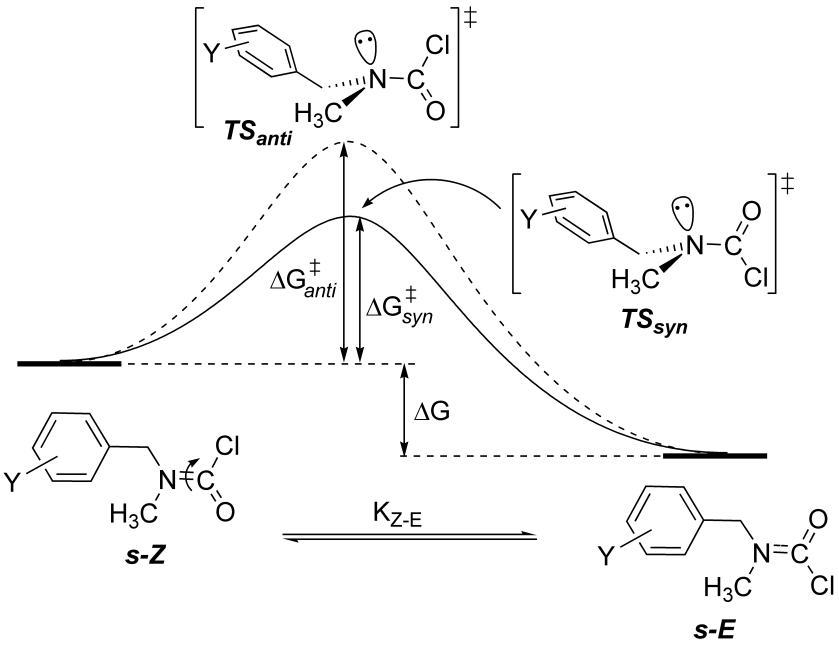


Figure 1: s-E/s-Z isomerization of structures **1a-h** through restricted rotation around the C(=O) – N bond.

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 Figure 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 ΔG for compound **1a** is available, based on previous NMR studies, and it compares very well with the theoretical result. The equilibrium constants $K_{Z\text{-}E}$ and the corresponding ratios s-Z : s-E are also shown in Table 1.

Table 1. Calculated thermodynamic and kinetic parameters for the restricted C – N bond rotation in carbamoyl chlorides **1a-h**. All values from *B3LYP/6-31+G(d)* calculations.

Chloride	ΔG_{298} [kcal/mol]	$K_{Z\text{-}E}$	s-Z : s-E	$\Delta G^{\neq}_{syn}$[a] [kcal/mol]	$\Delta G^{\neq}_{anti}$[a] [kcal/mol]	$\Delta\Delta G^{\neq}_{syn/anti}$ [kcal/mol]
1a	-0.4 *(-0.2)*[b]	1.97	34 : 66	16.2 *(17.1)*[b]	18.1	-1.9
1b	-0.6	2.78	26 : 74	15.9	17.8	-1.9
1c	-1.0	5.40	16 : 84	15.7	17.4	-1.7
1d	-0.6	2.53	28 : 72	15.8	17.7	-1.9
1e	-0.4	1.95	34 : 66	15.7	17.8	-2.1
1f	-0.4	1.95	34 : 66	16.3	18.4	-2.1
1g	-1.1	6.28	14 : 86	15.8	17.8	-2.0
1h	-0.4	2.04	33 : 67	16.0	17.8	-1.8

[a] Values for the s-Z to s-E conversion. [b] Italicized values in parentheses based on NMR studies, from Ref. [13].

Images of the stationary points for structure **1a** are shown in Figure 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 carbamoyl 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.

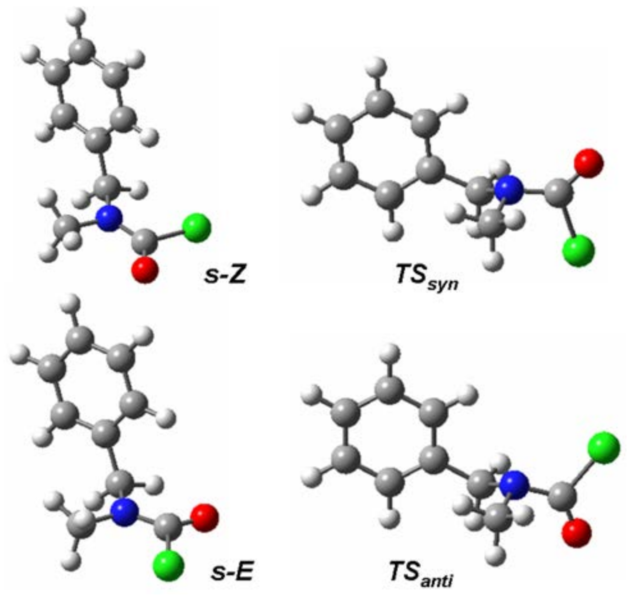


Figure 2. Ball-and-bond images of the stationary points for carbamoyl chloride **1a**. All structures from *B3LYP/6-31+G(d)* calculations

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, carbamates), the interconversion of rotamers can take place through one of two different transition states: TS_{syn} and TS_{anti} (Figure 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 *G2(MP2)//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-dimethylcarabamate 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]

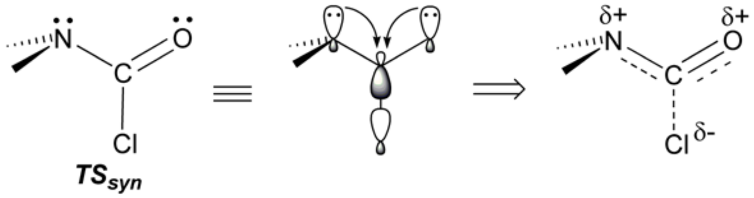


Figure 3. Stabilizing gauche effect in TS$_{syn}$, arising from orbital interaction of the lone pairs at the carbamoyl nitrogen and the carbonyl oxygen centers with the σ* orbital of the C – Cl bond.

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 σ* orbital of the C – Cl bond, as represented schematically in Figure 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.

Table 2. Selected calculated structural parameters for the optimized stationary points of carbamoyl chlorides **1a-h**. Results form *B3LYP/6-31+G(d)* calculations. Bond lengths in angstroms [Å]. Dihedral angles in degrees.

Structure		**N** – **C**(=O)	**Cl** – **C**(=O)	**C** = **O**	**Cl** – **C**(=O) – – **N** – **C**(H_3)	**C**(=O) – **C**(H_3) – – **C**(H_2) – **N**
	s-Z	1.35	1.83	1.21	-179.3	-4.2
1a	TS_{syn}	1.40	1.86	1.19	67.0	-27.8
	TS_{anti}	1.42	1.80	1.20	-116.2	-31.8
	s-E	1.35	1.82	1.21	0.6	-2.2
	s-Z	1.35	1.83	1.21	-179.1	-3.6
1b	TS_{syn}	1.40	1.86	1.19	67.1	-27.8
	TS_{anti}	1.41	1.80	1.20	-116.3	-31.9
	s-E	1.35	1.83	1.21	1.0	-2.3
	s-Z	1.36	1.83	1.20	-179.3	-4.7
1c	TS_{syn}	1.41	1.85	1.19	66.4	-28.0
	TS_{anti}	1.42	1.80	1.20	-116.6	-32.1
	s-E	1.36	1.81	1.21	1.5	-1.9
	s-Z	1.36	1.83	1.20	-179.3	-4.3
1d	TS_{syn}	1.41	1.85	1.19	66.4	-28.0
	TS_{anti}	1.42	1.80	1.19	-116.5	-32.0
	s-E	1.35	1.82	1.21	4.3	1.2
	s-Z	1.35	1.83	1.21	-179.0	-3.5
1e	TS_{syn}	1.40	1.86	1.19	67.3	-27.8
	TS_{anti}	1.41	1.80	1.20	-116.2	-32.0

	s-E	1.35	1.83	1.21	1.5	-1.5
	s-Z	1.35	1.83	1.21	-179.0	-3.3
1f	TS$_{syn}$	1.40	1.86	1.19	67.0	-27.8
	TS$_{anti}$	1.42	1.80	1.20	-116.3	-32.0
	s-E	1.35	1.82	1.21	3.3	-1.1
	s-Z	1.36	1.83	1.20	-179.2	-4.3
1g	TS$_{syn}$	1.40	1.85	1.19	66.6	-27.9
	TS$_{anti}$	1.42	1.80	1.20	-116.6	-32.1
	s-E	1.35	1.82	1.21	1.1	-2.6
	s-Z	1.36	1.82	1.20	-179.4	-4.2
1h	TS$_{syn}$	1.40	1.85	1.19	66.4	-27.9
	TS$_{anti}$	1.42	1.80	1.20	-116.3	-31.8
	s-E	1.36	1.82	1.21	-0.2	-3.1

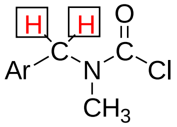
There are very few available experimental values on the thermodynamics and kinetics of the s-E/s-Z isomerization process in carbamoyl chlorides. Proton NMR studies of McArthur *et al.* on a series of N-alkyl-N-benzylcarbamoyl chlorides (variation of the alkyl group) revealed Gibbs free energy of activation values 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 N-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 values of other, similar structures? Barriers for amides are higher or comparable. Thus, reported calculated barriers 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] However, 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 kcal/mol and 14.9 kcal/mol were reported for methyl N,N-dimethylcarbamate and cyclohexyl N,N-dimethylcarbamate correspondingly.[5,6] DFT calculations on three *t*-butyl N-methylcarbamates, with an N-phenyl, N-2-pyridyl and N-2-pyrimidyl substituent correspondingly, 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 tetramethylurea 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) – N 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 $\Delta G^{\neq}_{syn}$ and $\Delta G^{\neq}_{anti}$ originates from the stabilizing gauche effect in TS_{syn}, lowering the energy of the latter.

Table 3. Theoretical and experimental chemical shift values for the benzylic (CH_2) hydrogen atoms of the s-Z and s-E rotamers of carbamoyl chlorides **1a**, **1c**, **1e** and **1g**. All computed values are from GIAO *B3LYP/6-311+G(2d,p)//B3LYP/6-31+G(d)* calculations, and are referenced to the chemical shift of TMS computed at the same level of theory. Experimental values are from spectra acquired in $CDCl_3$.



Chemical shift	**1a** s-E	**1a** s-Z	**1c** s-E	**1c** s-Z	**1e** s-E	**1e** s-Z	**1g** s-E	**1g** s-Z
theoretical	4.61	4.73	4.68	4.85	4.51	4.64	4.63	4.76
experimental[a]	4.58 *(4.60)*[b]	4.72 *(4.73)*[b]	4.69	4.84	4.51	4.65	4.58	4.72

[a] Values from Ref. [30]. All data from spectra acquired in $CDCl_3$. [b] Values from Ref. [13].

Theoretical NMR studies of N-benzyl-N-methylcarbamoyl chlorides: s-E and s-Z isomer shift assignment. In order to provide an unambiguous assignment of rotamer signals in the NMR spectra of the studied carbamoyl chlorides, we undertook a series of NMR calculations, results from which are shown in Table 3. Only the shift values for the hydrogens of the benzylic methylene group are listed, since they are clearly visible in the experimental spectra, and therefore particularly well suited for comparison. The theoretical results are in a remarkably good agreement with the experimental values[13,30], with differences no greater than 0.05 ppm, but in most cases even smaller. The computed shifts properly reflect what appears to be a clear trend, namely that the s-E rotamer in each of the cases exhibits an upfield shift for the signal of the benzylic group.

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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Supporting Information Available. Energies and thermodynamic parameters of all stationary points are summarized in Table S1.

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