JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2005; **18:** 310–314
Published online 5 October 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.855

Influence of methyl substituents on the stability of 1-aza-2-adamantanone, Kirby's most twisted amide

Kathleen M. Morgan,[1]* M. Logan Rawlins[2] and Margo N. Montgomery[1]

[1]Department of Chemistry, Xavier University of Louisiana, 1 Drexel Drive, New Orleans, Louisiana 70125, USA
[2]Department of Chemistry, College of William and Mary, P.O. Box 8795, Williamsburg, Virginia 23187, USA

Received 21 June 2004; revised 16 July 2004; accepted 16 July 2004

ABSTRACT: Hydrolysis and carbonyl hydration of adamantane-based twisted amide **1** were studied computationally. The importance of the bridgehead methyl substituents on these reactions was determined. The carbonyl hydration of **1** is structurally and energetically much like the hydration of a transition state to amide C—N bond rotation. However, hydrolysis of **1** to the amino acid is dependent on the bridgehead methyl substituents and less like hydrolysis of an amide transition state. Copyright © 2004 John Wiley & Sons, Ltd.
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KEYWORDS: twisted amide; amide hydrolysis; amide hydration; Thorpe–Ingold effect

INTRODUCTION

The importance of the amide functional group in organic chemistry and biochemistry is well established.[1] Most amides are planar and stabilized by the σ and π electron delocalization in the N—C—O region of the molecule (Fig. 1).[2,3] This stabilization is reflected in the $\sim$20 kcal mol^{-1} (1 kcal = 4.184 kJ) barrier to rotate the C—N bond from the planar conformation to the 90° rotated transition state.

A family of 'twisted' amides is known in which the structure of the amide causes a decrease in the interaction between the nitrogen lone pair and the carbonyl group.[4,5] Many of these twisted amides are polycyclic lactams having bridgehead nitrogen atoms. These amides have been shown to have unusual properties and reactivity. In many ways, highly twisted amides behave as amino ketones rather than amides; for example, protonation occurs on nitrogen rather than oxygen. The subject of this study, amide **1** (Fig. 2), has an IR absorbance at 1732 cm^{-1} and also reacts with an ylide in a Wittig reaction, both typical of a ketone or aldehyde but not an amide.[6,7]

We became interested in amide **1** because the amide is rotated 90° from planarity, as determined by crystallography,[6] and as such, it can be thought of as a stable model of the transition state to amide C—N bond rotation. Hydrolysis of amide **1** to the corresponding amino acid occurs rapidly at room temperature without catalysis. Even more striking, the carbonyl hydrate is an isolable solid.[6,8] The amide, amino acid and carbonyl hydrate exist as an equilibrium mixture in solution (Fig. 2), in which the composition and protonation state of the solvated species depend on the solvent and the pH of the medium.

**Correspondence to:* K. M. Morgan, Department of Chemistry, Xavier University of Louisiana, 1 Drexel Drive, New Orleans, Louisiana 70125, USA.
E-mail: kmmorgan@xula.edu
Contract/grant sponsor: Research Corporation; *Contract/grant number:* CC4113.
Contract/grant sponsor: National Institutes of Health; *Contract/grant number:* 7 R15 GM59037-02.

RESULTS AND DISCUSSION

We report the calculated energies of the remarkable hydrolysis and hydration reactions of amide **1**, and discuss whether the amide is a reasonable model of an amide rotational transition state. The unusual stability of **1** is certainly due in part to the thermodynamically favorable adamantane ring system,[7] but might also be influenced by the buttressing effects of the bridgehead methyl groups; Kirby *et al.* reported that the synthesis of an analog of amide **1** having just one bridgehead methyl substituent is substantially more difficult than the synthesis of **1**.[8] In this study, amide **1**, its amino acid and its carbonyl hydrate were all studied computationally in the gas phase. In addition, analogs with no, one and two methyl groups on the bridgehead positions (**1**–**6**, Fig. 3) were calculated.

Amide structures

Six twisted amides were calculated (Fig. 3), having three (**1**), two (symmetrical) (**2**), two (asymmetric) (**3**), one

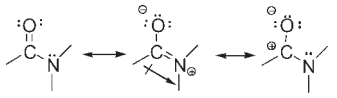

Figure 1. Electron delocalization in planar amides

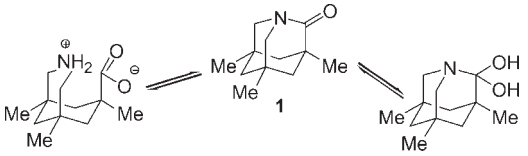

Figure 2. Reactions of twisted amide **1**[6]

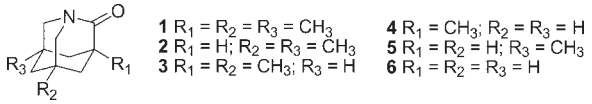

Figure 3. The twisted amides studied

(symmetrical) (**4**), one (asymmetric) (**5**) and no (**6**) bridgehead methyl groups. At the B3LYP/6–31+G* level of theory,[9] and in the gas phase, all six amides are similar and independent of the number or position of the methyl groups. In all cases, the C═O bond length was 1.21 Å and the amide C—N bond length was 1.46 Å. These data are in agreement with crystallographic data obtained by Kirby *et al.* on **1**, in which r(C═O) = 1.196 Å and r(C—N) = 1.475 Å.[6] Also, as in the crystal structure, the calculated carbonyl groups are planar, with the sum of the bond angles 360 ± 0.1°. The calculated pyramidalization of the nitrogen atoms differs slightly from the experimental value, with the sum of the bond angles of 327.6 ± 0.5° versus 325.7°, respectively.

Two reference compounds were also calculated, *N*-methylcaprolactam and *N*,*N*-dimethylacetamide (DMA), both of which have normal, planar amide groups. In *N*-methylcaprolactam, the C═O bond length was 1.23 Å and the C—N bond length was 1.38 Å. In this simple tertiary lactam, both the carbonyl carbon and nitrogen are planar, as determined by the sum of the angles. Three conformations of DMA were also studied, the planar conformer and two transition states. The transition state with the N lone pair *syn* to the carbonyl is analogous to the twisted amide structure, and the transition state with the N lone pair *anti* to the carbonyl is lower in energy by 3.1 kcal mol^{-1}. The C═O bond lengths were 1.23, 1.21 and 1.21 Å for the planar, *syn* and *anti* structures, respectively, and the C—N bond lengths were 1.38, 1.45, and 1.46 Å. The nitrogen in the planar conformer and all carbonyl carbons are planar. The nitrogen atoms in the transition states are pyramidalized, with the sum of the angles of 338.6° (*syn*) and 332.7° (*anti*), but noticeably less so than in **1**–**6**. Clearly, the twisted amides are structurally very much like the *syn* amide rotational transition state.

In addition, the electron densities of amide **1** and the three conformations of DMA were also compared. The

Table 1. Calculated charge densities of twisted amide **1** and DMA

	N	C	O
Amide **1**	−0.587	0.755	−0.528
DMA, planar	−0.513	0.680	−0.645
DMA, *syn* transition state	−0.606	0.731	−0.526
DMA, *anti* transition state	−0.622	0.734	−0.554

Weinhold–Reed natural population analysis charges[10] were obtained using the B3LYP/6–31+G* structures. Not surprisingly, the electron distribution in **1** is most similar to the *syn* transition state, as shown in Table 1.

The molecular orbitals of amide **1**, planar DMA and the *syn* DMA transition state were also compared (we thank a referee for suggesting this analysis). The HOMO of DMA has a π-type antibonding interaction between the carbonyl and C—N bonds. The N—C—O in-phase π-type overlap is observed in the HOMO-2 orbital. The orbitals for the DMA transition state and twisted amide **1** are significantly different from the planar amide, and similar to each other. The HOMO of both of these twisted molecules has a large lobe representing the nitrogen lone pair and smaller but significant antiperiplanar electron density on the *N*-methyl C—H in the DMA transition state and the corresponding C—C bonds in the adamantane skeleton. The HOMO-10 orbital in both molecules shows π-type in-phase N—C—O delocalization. Interestingly, in the DMA transition state, the orientation is perpendicular to the lone pair on nitrogen, whereas in amide **1**, the orbital includes the nitrogen lone pair and is perpendicular to the C═O π bond.

Amide hydrolysis to the amino acid

The calculations do not apply a solvation model, hence neutral, non-zwitterionic amino acids are favored in the gas phase. Two amino acid conformations were considered (Fig. 4). In the lower energy conformation, hydrogen bonding occurs between $CO_2H\cdots$:N and the bottom cyclohexane ring is substantially flattened. The other conformation is less stable by 1.4 kcal mol^{-1} in the trimethyl series, and has the NH hydrogen pointing towards the carboxyl group; however, the NH$\cdots$:O═C distance is > 2.4 Å, hence hydrogen bonding here is not

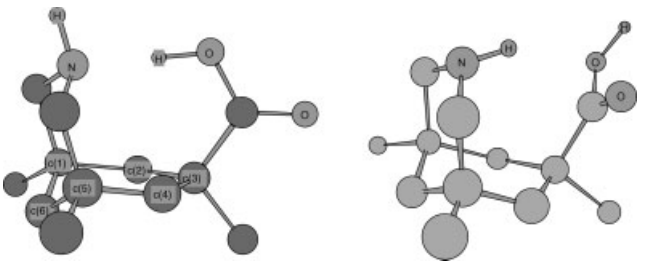

Figure 4. Conformations of the amino acids

Table 2. Enthalpies of amide hydrolysis and carbonyl hydration (kcal mol^{-1})[a]

Amide	ΔH(hydrolysis)	ΔH(hydration)
1 3 methyls	−7.6	−3.6
2 2 methyls, symmetrical	−11.5	−4.6
3 2 methyls,asymmetric	−8.6	−3.3
4 1 methyl, symmetrical	−9.7	−3.2
5 1 methyl, asymmetric	−12.4	−4.3
6 0 methyls	−13.5	−4.3

[a] B3LYP/6–31+G*//B3LYP/6–31+G*. ZPE are scaled by 0.9804.[17]

as important. In solution, with intermolecular hydrogen bonding possible, this alternative conformation may become more stable.

The enthalpy of amide hydrolysis to the more stable amino acid conformer is dependent on both the number and position of methyl substituents present on the adamantane skeleton (Table 2). At one extreme when three bridgehead methyl groups are present, hydrolysis to the amino acid is exothermic, −7.6 kcal mol^{-1}. At the other extreme with no bridgehead methyl groups, the reaction is even more exothermic, −13.5 kcal mol^{-1}, a difference of 5.9 kcal mol^{-1}.

During the formation of the more stable amino acid, the adamantane ring system opens and the amine and acid groups spread apart to allow the beneficial hydrogen bonding to take place (Fig. 5). Recent calculations suggest that in the gas phase, intramolecular amide hydrogen bonds, albeit NH···:O═C rather than N:···HO, are typically worth 7–9 kcal mol^{-1}.[11] The structure of the hydrogen-bonded amino acid region of the molecule is virtually the same for the six amino acids investigated. The hydrogen bonded N:···HO distance is 1.65–1.66 Å, the H—O bond length is 1.02 Å, the O—C bond length is 1.34 Å and the C═O bond length is 1.22 Å.

The energy of amide hydrolysis is most sensitive to the presence of a methyl substituent on the bridgehead carbon adjacent to the carbonyl group. Using a hand-held Dreiding-type model, it appears that when the adamantane ring system opens up and the base cyclohexane ring flattens, this bridgehead methyl encounters a hydrogen on the opposing methylene group, leading to strain. This bridgehead methyl is present in amides **1**, **3** and **4**, the three molecules with the least favorable hydrolysis enthalpies (Group 1). This methyl is absent in the remaining molecules (Group 2). One would therefore expect that the cyclohexane ring would flatten less in the Group 1 molecules.

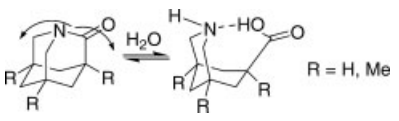

Figure 5. Structural deformations on amide hydrolysis

It is true that the extent of ring flattening depends on whether a molecule is in Group 1 or Group 2, but not as predicted. The biggest difference between the Group 1 and Group 2 amino acids is in the C1—C2—C3—C4/C5—C4—C3—C2 dihedral angles (numbering given in Fig. 4). In Group 1 molecules, the carboxylic acid-containing bridge is substantially flattened, with the dihedral angles ranging from 10.9 to 13.6°. In the Group 2 amino acids, the ring is puckered as in a normal, albeit flattened cyclohexane chair, with dihedral angles ranging from 21.5 to 22.7°. The remaining dihedral angles vary less between Group 1 and 2 molecules; C3—C4—C5—C6 ranges from 36.4 to 40.4° in Group 1 and from 41.6 to 45.3° in Group 2, and C4—C5—C6—C1 ranges from 64.1 to 66.9° in Group 1 and from 63.9 to 66.5° in Group 2.

These results are counterintuitive; one would expect that the molecules in Group 1 would flatten less owing to the expected non-bonded strain, yet they are observed to flatten more. Even with the extreme flattening observed in the amino acid having three bridgehead methyl groups, there is no steric strain between the bridgehead methyl and the opposing methylene group. The closest H—H non-bonded distance here is 3.02 Å.

It is difficult to pinpoint the reasons why Group 1 molecules flatten more than Group 2 molecules. However, the increased chair deformation of the Group 1 molecules leads to greater torsional strain, thereby reducing the driving force for the hydrolysis, as observed. Further, among the Group 1 compounds, the greater the flattening observed, the less exothermic is the hydrolysis reaction.

The bridgehead methyl substituents appear to exert subtle but important pressure on the structures. The amide and amino acid having three methyl substituents are larger overall. For example, the intra-bridgehead distances in the amide are 2.55–2.56 Å, whereas the amide with no methyl groups has distances of 2.52 Å. Similar differences are observed in the amino acids. Carbon–carbon bonds are also slightly longer in the molecules with more bridgehead methyl substituents. A second, and probably more important, factor is the outward bending of the carboxylic acid group. This bending is less when the C3 bridgehead methyl group is present. The C(O)—C(bridgehead)—C(methyl) angle is 106.7–106.8° with the methyl present, and the analogous C(O)—C(bridgehead)—H angle is 101.3–101.5° in the amino acid without methyls. There is certainly a strong driving force to obtain the ideal intermolecular hydrogen bonding in this gas-phase structure. Perhaps the bridgehead methyl prevents the outward flexing of the carboxylic acid group, thereby requiring the unexpected extreme ring flattening. Hence there appear to be several small structural implications of the bridgehead methyl group. This type of buttressing to promote ring formation is well known,[12,13] and therefore the hydrolyses of the twisted amides provide another example of the Thorpe–Ingold effect.

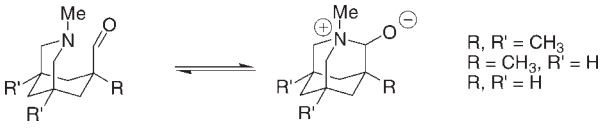

Figure 6. Aminoaldehyde equilibrium

The bridgehead methyl substituents are also important, although less so, in the formation of the higher energy amino acid conformations. Hydrolysis of the amide **1** with three bridgehead methyls is $-6.2\,\text{kcal mol}^{-1}$, whereas hydrolysis of amide **6** without bridgehead methyls is $-10.5\,\text{kcal mol}^{-1}$. The same C3 bridgehead methyl group again appears to be important, inhibiting rotation of the carboxylic acid group necessary for intramolecular stabilization. In the trimethyl compound, the NH$\cdots$:O=C distance is 2.49 Å, and without methyls present, the carbonyl oxygen rotates noticeably inward, and the distance is 2.42 Å.

Not all reactions in which an adamantane ring system is opened and closed are sensitive to bridgehead methyl substituents. Davies *et al.* recently described a study involving a series of three related amino aldehydes and their cyclized hemiaminal zwitterions (Fig. 6).[14] Contrary to their expectations, the equilibrium constants measured in anhydrous CD_2Cl_2 are not greatly influenced by the methyl substituents; ΔH° is $-3.7\,\text{kcal mol}^{-1}$ with three methyls, $-3.9\,\text{kcal mol}^{-1}$ with one methyl and $-4.6\,\text{kcal mol}^{-1}$ with no methyl groups present. In keeping with the ideas described above, the aminoaldehyde is not expected to spread open as much as the amino acids because hydrogen bonding is not an issue. Further, the smaller aldehyde group would experience less steric hindrance from the C3 bridgehead methyl group. Overall, it is not unreasonable that this reaction is less sensitive to the bridgehead methyl substituents.

Amide hydration to the carbonyl hydrate

Only one conformation of the carbonyl hydrates was studied, with anomeric stabilization of the geminal diol (Fig. 7). The distance between the nitrogen and the nearest OH hydrogen is 2.43 Å. Kirby *et al.* reported a crystal structure for the hydrochloride salt of the hydrate in which the nitrogen is protonated and both hydroxyl protons interact with the chloride.[8] These two molecules differ sufficiently that comparisons are not germane.

As seen in Table 2, the energy of carbonyl hydration is much less dependent on the number and position of methyl substituents. This is not unexpected, considering that the adamantane ring system is not opened up during this reaction. The exothermicity observed in these amide hydration reactions is of the same magnitude as the calculated gas-phase hydration of acetaldehyde,[15] and is due to the electron-withdrawing effect of the nitrogen adjacent to the carbonyl group. It is curious that the twisted amide hydrate is stable, but the hydrate of acetaldehyde is not.

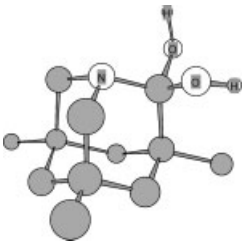

Figure 7. Calculated structure of the carbonyl hydrate

Comparisons with *N*-methylcaprolactam and *N, N*-dimethylacetamide

Our hypothesis was that the twisted amide **1** was destabilized by $\sim 20\,\text{kcal mol}^{-1}$, the energy commonly associated with the amide rotational barrier. Hence, the reactions of **1** should be more exothermic by $20\,\text{kcal mol}^{-1}$ compared with planar amide reference compounds, if in fact **1** fairly represents a transition state. Further, the reactions of **1** should be similar to those of DMA transition states.

Three conformations of the amino acid generated from *N*-methylcaprolactam were studied. Two fully extended structures were considered and had hydrolysis enthalpies of 2.1–2.9 kcal mol^{-1}. Attempts were made to obtain a cyclic structure in which hydrogen bonding was present. The all-*gauche* structure that was found does not have hydrogen bonding; the N:$\cdots$HO distance is 3.93 Å. The enthalpy of hydrolysis to this conformation is $6.0\,\text{kcal mol}^{-1}$. The hydrolysis enthalpy of planar DMA is $1.2\,\text{kcal mol}^{-1}$. The hydrolyses of these planar reference amides are not $20\,\text{kcal mol}^{-1}$ more exothermic than hydrolysis of **1**. This suggests that hydrolysis of **1** is substantially different than hydrolysis of an amide transition state, owing primarily to strain in the amino acid product. Further, hydrolysis of the *anti* transition state from DMA has a reaction enthalpy of $-14.8\,\text{kcal mol}^{-1}$, and hydrolysis of the *syn* transition state, the one more closely resembling the twisted amide, $-17.9\,\text{kcal mol}^{-1}$. Again, the hydrolyses of the twisted amides do not fully reflect the expected destabilization, although the twisted amide having no bridgehead substituents comes close.

Hydration of *N*-methylcaprolactam and DMA was also studied. Two conformations of the lactam hydrate were found, one with the *N*-methyl group equatorial and the other axial. The hydration enthalpies are 15.4 and $17.4\,\text{kcal mol}^{-1}$, respectively. Two conformations of the DMA hydrate were found. The lower energy hydrate has the nitrogen lone pair oriented *syn* to the former carbonyl carbon, and is analogous to the twisted amide hydrates. The hydration enthalpy of the *syn* DMA transition state to this hydrate is $-5.1\,\text{kcal mol}^{-1}$, similar to the hydration enthalpies of the twisted amides. The higher energy

hydrate, destabilized by 1.1 kcal mol^{-1}, is similar to the hydrate found for *N*-methylcaprolactam. The hydration enthalpy from planar DMA to this transition state is 15.2 kcal mol^{-1}, like that observed in *N*-methylcaprolactam. The hydration of **1** and the other twisted amides studied is similar both structurally and energetically to hydration of an amide transition state, albeit the higher energy transition state, and $\sim$20 kcal mol^{-1} more favorable than hydration of the planar reference compounds. This suggests that hydration of **1** is much like that for an amide transition state.

COMPUTATIONAL METHODS

All calculations were performed using Gaussian 98W, Version 5.4.[16] Geometries were optimized at the B3LYP/6–31+G* level of theory.[9] A vibrational frequency analysis was also performed using this method, and all molecules were found to have zero imaginary frequencies except the transition states of DMA, which were each found to have one. Zero-point energies were scaled by 0.9804.[17] Calculations were also performed using B3LYP/6–31G* methodology, and the structures and energy trends are similar. Without diffuse functions, the calculated reaction enthalpies are more exothermic, with amide hydrolysis ranging from -12.1 to -17.6 kcal mol^{-1} and amide hydration ranging from -8.2 to -9.1 kcal mol^{-1}. Because diffuse functions are important in the description of hydrogen bonds, the results of the B3LYP/6–31+G* calculations are reported.

CONCLUSIONS

The use of amide **1** as a model of the transition state to amide C—N bond rotation carries some risk. Carbonyl hydration of **1** is similar both structurally and energetically to hydration of the *syn* transition state to C—N bond rotation. However, in the case of amide hydrolysis to the amino acid, the adamantane ring system is opened, and the buttressing effects of the bridgehead methyl substituents destabilize the amino acid and lead to an artificial stabilization of the amide. In this case, amide **1** behaves less like the amide rotational transition state.

Supplementary material

Cartesian coordinates, energies and zero-point energies of all molecules calculated (23 pages) are available in Wiley Interscience.

Acknowledgements

We thank Research Corporation (Grant CC4113) and the National Institutes of Health (Grant 7 R15 GM59037–02) for support of this research. We also thank Professor Christopher Hadad (Ohio State University) and Professor Anthony Kirby (Cambridge University) for helpful discussions.

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