The resonance model in amides: a combined crystallographic and *ab initio* investigation†

David Quiñonero, Antonio Frontera,* Magdalena Capó, Pau Ballester, Guillem A. Suñer, Carolina Garau and Pere M. Deyà*

Departament de Química, Universitat de les Illes Balears, 07071 Palma de Mallorca, Spain. E-mail: tonif@soller.uib.es; Fax: +34 971 173 498

Received* (*in Strasbourg, France*) *10th October 2000, Accepted 23rd November 2000
First published as an Advance Article on the web 22nd January 2001

The resonance model in amides has been questioned based on the changes that occur during the rotation of the C–N bond. The geometrical changes, electron population and electrostatic potentials calculated during the rotation have been used to propose that the oxygen atom does not participate to a significant extent in the rotational barrier. Our results based on X-ray analysis and *ab initio* calculations reveal that the resonance model is adequate to explain the properties of amides and show the role that the oxygen atom plays in the rotation.

Internal rotation in amide C–N bonds has been extensively studied by means of theoretical calculations.[1–3] Considering the previously reported results, the question concerning the role played by the oxygen atom on going from the ground state to the C–N rotated saddle point remains unsatisfactorily answered. Whereas Wiberg *et al.*[2] suggest that the oxygen atom is merely a spectator, others[3] support the more classical thesis of the resonance theory of Pauling.

Based on *ab initio* (MP2/6-31G*) calculations on formamide C–N rotation, Wiberg and colleagues explain that the electronegative oxygen atom leads to polarization of the C=O bond in the sense $C^{+}=O^{-}$. In the planar form, the nitrogen atom assumes an sp^2 hybridization and its lone pair can interact with the electron deficient carbon atom. This stabilization is lost upon a 90° rotation around the C–N bond. Wiberg's explanation is based on the following evidence: first, the carbonyl bond length decreases by only 0.01 Å whereas the C–N bond length increases by 0.08 Å upon a 90° rotation, indicating that the main changes are in the C–N bond and that the C–O bond is unaffected by rotation. Second, the electron population (AIM[4]) at the nitrogen atom was found to be greater in the ground state than at the saddle point. The electrons were taken from the carbon, and the electronic population at the carbonyl oxygen atom was almost unchanged during the rotation. Third, the kinetic energy between the atoms in the structures connecting the planar and saddle point conformers were evaluated using Bader's theory of atoms in molecules.[4] Again, most of the changes involve only the carbonyl carbon and the amide nitrogen atoms, while the changes at the carbonyl oxygen atom are small. It is worth noting that there is not any experimental evidence supporting Wiberg's model. However, both models (resonance and Wiberg's) are able to explain the well-known amide reactivity,[5] although Brown *et al.*[3b] have used the relationship between amidic distortion and ease of hydrolysis in base to support the resonance theory for amides. All evidence put forth by Wiberg *et al.* was mostly based on *ab initio* calculations of formamide at the MP2/6-31G* level, which has been found to give bond lengths and angles in good agreement with experimental data.[6] Structural and electronic properties of saddle points are not experimentally observable quantities and with it are all the uncertainties attached to experimentally unverifiable parameters. If the method is not accurate enough in determining the C=O distance at the saddle point, all the proofs and data could be worthless. An erroneous C=O distance could affect not only geometrical changes upon rotation, but also bond orders, electron populations, *etc.*

It is quite clear that without the results of crystallographic experiments, molecular modeling would at best have been a highly speculative activity. There have been major advances in the accuracy of theoretical calculations, nevertheless many researchers will wish to refer their results to crystallographic experiments, if available. Crystal structures are so rich in information that the systematic analysis of their geometry is able to reveal effects that had not been noticed by the original authors; this is specially true for small molecules, which are often studied simply to determine their chemical composition.

Recently, Kirby *et al.*[7] have reported the preparation, crystal structure and some chemistry of 1-aza-2-adamantanone, the most twisted amide, in which overlap of the lone pair on the nitrogen atom with the π system of C=O is prevented by the rigid geometry of the compound. This structure can be considered as a real model of a saddle point (rotated form) of a regular amide that can be studied experimentally. The X-ray analysis of 1-aza-2-amantanone shows that the carbonyl group is strictly planar and the nitrogen atom is pyramidal. The N–C and C=O bond lengths are 1.475(11) and 1.196(5) Å, substantially longer and shorter, respectively, than expected.[8]

In this paper, we report a study using the Cambridge Structural Database (CSD)[9] to show the influence of the rotation of the C–N bond in amides on the C=O distance as expected by the resonance model description. The CSD appeared to us to be a convenient and reliable storehouse for geometrical information. The utility of small-molecule crystallography and the CSD in analyzing geometrical parameters has been clearly established.[10] We also report *ab initio* (MP2/6-31G*) calculations on 1-aza-2-adamantanone. As stated above, Wiberg *et al.*[2] have used this level of theory to demonstrate that the C–O distance is not significantly affected by the rotation of the C–N bond in formamide. However, our results demonstrate that this level of theory is unable to reproduce

† Electronic supplementary information (ESI) available: cartesian coordinates and energies for the optimized structures of 1-aza-2-adamantanone, formamide and its rotated forms. See http://www.rsc.org/suppdata/nj/b0/b008260k/

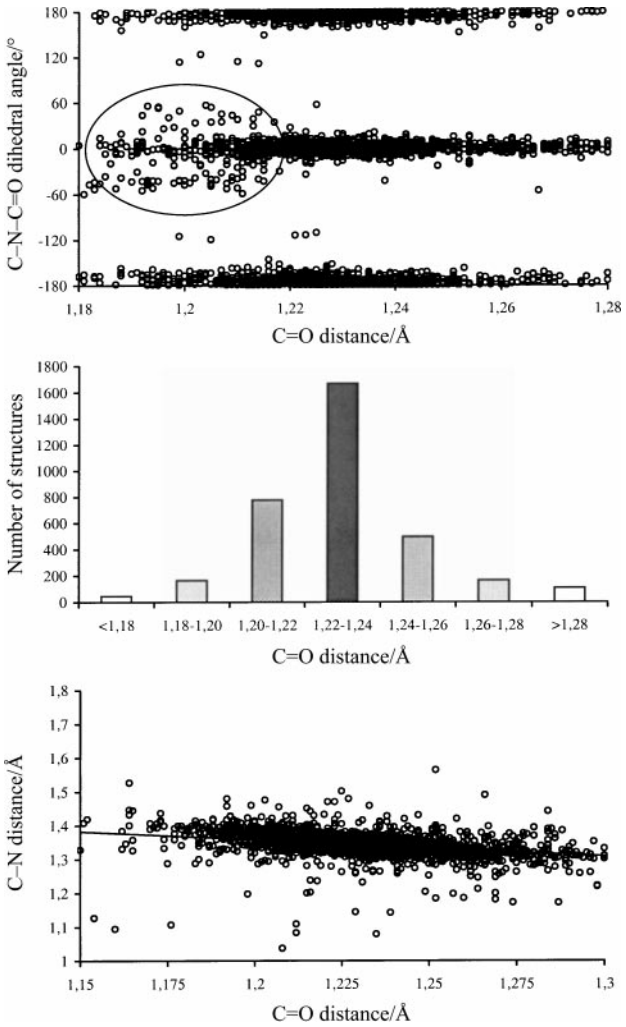

Fig. 1 Scatterplots of C=O distance *vs.* C–N–C=O dihedral angles (top) and C–B distances (bottom) and histogram of the C=O bond length for 3274 structures (3426 amido groups) taken from the CSD.

accurately the geometrical characteristics of 1-aza-2-adamantanone which will be mainly influenced by π effects.[11] Furthermore, the C=O distance predicted by *ab initio* calculations on 1-aza-2-adamantanone is significantly larger than the experimental one. Keeping in mind the limitations on the comparison of structures optimized in the gas phase to those in the

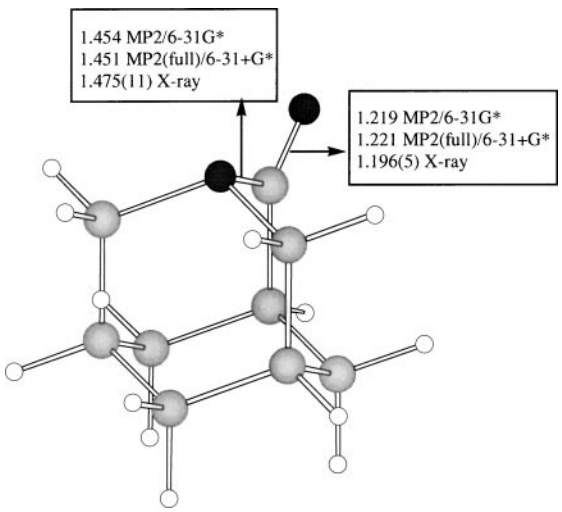

Fig. 2 *Ab initio* optimized structure of 1-aza-2-adamantanone. Distances are in Å.

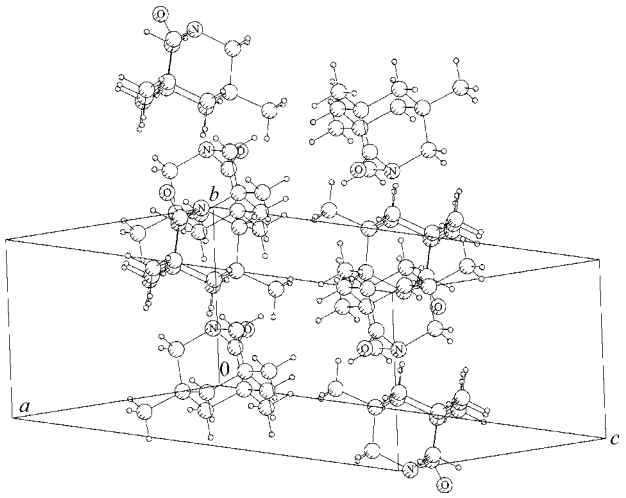

Fig. 3 Packing diagram of 1-aza-2-adamantanone, showing all molecules within the unit cell and those by extending it by a range of $+b$.

crystalline state,[12] both are expected to give similar trends as far as coupled geometry perturbations are concerned. To tackle this issue we give details about the crystal packing of 1-aza-2-adamantanone in order to analyze its molecular environment. Moreover, we report results obtained from ^{17}O NMR theoretical calculations on formamide and its rotated form. Dahn *et al.*[13] have shown that the chemical shift values in ^{17}O NMR spectra are very clearly different for doubly (=O) and singly (–O–) bonded oxygen atoms and that both, but particularly the former, are very sensitive to electronic influences and resonance effects. The ^{17}O NMR technique is a valuable tool to probe π-bond order or π-electron density around oxygen atoms. In addition, Yamada[14] has shown the relationship between C(O)–N twist angles obtained by X-ray crystallographic analysis and experimental ^{17}O NMR chemical shifts in a series of twisted amides.

Computational methods

Geometries (see ESI) were optimized at the MP2/6-31G* and MP2(full)/6-31+G* levels by using the GAUSSIAN 98 program package.[15] Diffuse functions were included in order to treat the lone pairs properly.[16] Absolute NMR shieldings were calculated using the GIAO method[17] at MP2/6-311+G**//MP2(full)/6-31+G*.

Results and discussion

Fig. 1 shows a scatterplot of the C–N–C=O dihedral angle of 3274 X-ray structures taken from the CSD. There are around 15 000 X-ray organic structures with amido groups in the CSD, but only those complying with the following requisites were selected: first, the substituents of the nitrogen atom should be sp^3 carbon atoms in order to avoid additional conjugation of the nitrogen atom lone pair with sp^2 groups (C=C, C=O, C=N, *etc.*). Second, an sp^3 carbon atom should be attached to the carbonyl group in order to avoid conjugation of the C=O that could interfere with the C=O distance upon distortion of the amino group. It can be seen from the histogram present in Fig. 1 that the C=O distance with the most structures represented is 1.22–1.24 Å. This value is in agreement with the computed distance for formamide (1.224 Å) at the MP2/6-31G* level of theory. A more important finding is that most structures with a dihedral angle far from 0 or 180° (characteristic of a nitrogen atom with sp^3 character) have a C=O distance <1.22 Å. Furthermore, the most distorted amides are in the region between 1.19 and 1.21 Å (see Fig. 1), giving rise to the following conclusion: the rotation around

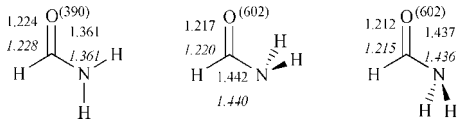

Fig. 4 ^{17}O NMR chemical shifts (in parenthesis) and distances for formamide and its rotated forms in ppm relative to water and Å, respectively. Distances in italics correspond to MP2/6-31+G* optimized structures.

the C–N bond has a remarkable influence on the C=O distance, supporting the resonance model. A scatterplot (Fig. 1) of the C–N distance *vs.* the C=O distance of the 3274 X-ray structures confirms that both distances behave the same way as in conjugated π-systems.

The MP2/6-31G* optimized geometry of 1-aza-2-adamantanone is shown in Fig. 2. The calculated C=O distance is 1.219 Å, close to that calculated for the rotated formamide at the same level of theory (1.212 Å), but far away from that obtained by X-ray analysis [1.196(5) Å]. Therefore, this level of theory seems to fail for rotated amides, and is unable to describe accurately the change in the C=O distance upon either rotation or distortion of the C–N bond. The use of diffuse functions does not improve the agreement between theoretical and experimental distances in 1-aza-2-adamantanone, as shown in Fig. 2. The molecular environment of 1-aza-2-adamantanone has been analyzed by exploring it in the crystal *via* packing diagrams (see Fig. 3).[18] As a result, we have not noticed any significant perturbation of the amido group. We have not found any intermolecular contact less than the sum of the van der Waals radii.

The ^{17}O NMR data of formamide are shown in Fig. 4. The calculated ^{17}O NMR chemical shift of formamide is 390 ppm, in acceptable agreement with the experimental value[13a] of 304 ppm.[19] The 90° rotated form of formamide gives a computed chemical shift of 602 ppm, close to the experimental value of acetone (569 ppm). These results confirm that there is a substantial change in the C=O bond upon rotation about the C–N bond. It is clear that the carbonyl group is not a spectator and is an active participant in the C–N rotation.

Bearing in mind the limitations of any qualitative model, the present results support the validity of the amide resonance model and provide an explanation for the apparent independence of the C=O bond length on the C–N rotation.

Acknowledgements

Gratitude is expressed to the DGICYT (project PB98-0129) for financial support. We thank the Centre de Supercomputació de Catalunya (CESCA) for computational facilities. A. F. thanks the MEC for a post-doctoral grant. D. Q. thanks the Universitat de les Illes Balears for a predoctoral fellowship.

References and notes

1 (*a*) N. A. Burton, S. S.-L. Chiu, M. M. Davidson, D. V. S. Green, I. H. Hillier, J. J. McDouall and M. A. Vincent, *J. Chem. Soc., Faraday Trans.*, 1993, **89**, 2631; (*b*) L. F. Olson, Y. Li, K. N. Houk, A. J. Kresge and L. J. Schaad, *J. Am. Chem. Soc.*, 1995, **117**, 2992.

2 (*a*) K. B. Wiberg and K. E. Laidig, *J. Am. Chem. Soc.*, 1987, **109**, 5935; (*b*) K. B. Wiberg and C. M. Breneman, *J. Am. Chem. Soc.*, 1992, **114**, 831; (*c*) K. B. Wiberg, C. M. Hadad, P. R. Rablen and J. Cioslowski, *J. Am. Chem. Soc.*, 1992, **114**, 8644; (*d*) K. B. Wiberg and P. R. Rablen, *J. Am. Chem. Soc.*, 1995, **117**, 2201.

3 (*a*) G. Fogarasi and P. G. Szalay, *J. Phys. Chem. A*, 1997, **101**, 1400; (*b*) A. J. Bennet, Q.-P. Wang, H. Slebocka-Tilk, V. Somayaji, R. S. Brown and B. D. Santarsiero, *J. Am. Chem. Soc.*, 1990, **112**, 6383.

4 (*a*) R. F. W. Bader, *Acc. Chem. Res.*, 1985, **18**, 9; (*b*) R. F. W. Bader, *Atoms in Molecules: A Quantum Theory*, Oxford University Press, Oxford, UK, 1990; (*c*) R. F. W. Bader, *Chem. Rev.*, 1991, **91**, 893.

5 (*a*) M. B. Robin, F. A. Bovey and H. Basch, in *The Chemistry of Amides*, ed. J. Zabicky, Wiley-Interscience, London, UK, 1970; (*b*) P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, UK, 1983.

6 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986, ch. 6.

7 A. J. Kirby, I. V. Komarov, P. D. Wothers and N. Feeder, *Angew. Chem., Int. Ed.*, 1998, **37**, 785.

8 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.

9 http://www.ccdc.cam.ac.uk

10 (*a*) A. Nangia, K. Biradha and G. R. Desiraju, *J. Chem. Soc., Perkin Trans. 2*, 1996, 943; (*b*) G. R. Desiraju, *Crystal Engineering. The Design of Organic Solids*, Elsevier, Amsterdam, The Netherlands, 1989.

11 The shift in π density towards nitrogen upon rotation of the C–N bond induces a concomitant countermigration of the σ density to the carbon atom. This σ/π equilibrium has been observed and rationalized before. See: (*a*) A. Gobbi and G. Frenking, *J. Am. Chem. Soc.*, 1993, **115**, 2362; (*b*) A. Gobbi, P. J. MacDougall and G. Frenking, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1001; (*c*) T. S. Slee and P. J. MacDougall, *Can. J. Chem.*, 1988, **66**, 2961.

12 (*a*) H. B. Bürgi and J. D. Dunitz, *Acc. Chem. Res.*, 1983, **16**, 153; (*b*) J. D. Dunitz and A. Gavezzotti, *Acc. Chem. Res.*, 1999, **32**, 677.

13 (*a*) H. A. Christ, P. Diehl, H. R. Schneider and H. Dahn, *Helv. Chim. Acta*, 1961, **44**, 865; (*b*) H. Dahn and M.-N. Ung-Truong, *Helv. Chim. Acta*, 1987, **70**, 2130.

14 S. Yamada, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1131.

15 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, O. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Rashavachari, J. B. Forestman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., GAUSSIAN 98, Rev. A.7, Pittsburgh PA, 1998.

16 T. Clark, J. Chandrasekhar, G. W. Spitznagel and P. v. R. Schleyer, *J. Comput. Chem.*, 1983, **4**, 294.

17 K. Wolinski, J. F. Hinto and P. Pulay, *J. Am. Chem. Soc.*, 1990, **112**, 8251.

18 Crystal packing diagrams have been generated using the PLUTO program: S. Motherwell and W. Clegg, PLUTO, Program for Constructing Molecular and Crystal Structures, University of Cambridge, Cambridge, UK, 1978.

19 Taking into account the deshielding influence of the hydrogen bonds in water.