

Solvent effects on the internal rotation barrier around the C–N bond and ^{14}N NMR shielding of 2-amino-3-mercapto propionamide: continuous set of gauge transformation calculations using a polarisable continuum model

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Solvent effects on rotational barriers of 2-amino-3-mercapto-propionamide, an amide derived from cysteine, have been investigated at HF and MP2 levels of theory using a polarisable continuum model (PCM) of solvent. The predicted barrier in the gas phase increases by increasing the polarity of solvents. It was shown that the observed solvent-induced shielding variation is more strongly related to the intensity of the solvent reaction field rather than to the change of molecular geometry induced by the solvent.

Keywords: 2-amino-3-mercapto propionamide, barrier internal energy, NMR shielding, solvent effect, ab initio

Proteins play crucial roles in virtually all biological processes. A striking characteristic of proteins is that they have well-defined three-dimensional structures. A stretched-out or randomly arranged polypeptide chain is devoid of biological activity. Biological activity arises from conformation. The potential for rotation about the C–N bond in amides is of fundamental importance for understanding of the conformation of proteins, particularly since molecular dynamics simulations of the structure of these macromolecules require accurate potentials to model this rotation. In this paper we address a number of aspects of C–N bond rotation in 2-amino-3-mercapto propionamide, an amide derived from the amino acid cysteine, which are relevant to modelling peptides both in the gas phase and in solution. *Ab initio* calculation of nuclear magnetic shielding has become an indispensable aid in the investigation of molecular structure and accurate assignment of NMR spectra of compounds.

The data from the experimental studies constitute a database of experimental nitrogen shielding that can be utilised to evaluate the reliability of NMR Calculations for systems in solution. The solvation effect is taken into account via the self consistent reaction field (SCRF) method. This method is based on the Onsager reaction field theory of electrostatic solvation. The effect of polarisation of the solvent continuum is represented numerically.

In 1997, a new PCM method called the integral equation formulation^{30,31} was introduced. In this method, diverse types of dielectrics (standard isotropic liquids, intrinsically anisotropic media like liquid crystals and solid matrices and ionic solutions) are treated in a single common approach. All PCM calculations in this report have been performed using this formalism as implemented in GAUSSIAN 98³². The unavailability of PCM-gauge invariant atomic orbitals^{27,28} in Gaussian 98 has restricted us to exploit PCM-CSGT²⁷ in nuclear shielding calculations.

Computational details

The *ab initio* molecular calculations were carried out by the use of the GAUSSIAN 98 program. Geometry optimization in the gas phase for 2-amino-3-mercapto propionamide was performed at the Hartree-Fock (HF) level with the 6-31G(d), 6-31++G and 6-31++G(2d, p) basis sets.

Direct and indirect contributions to the total solvation effects were examined. Direct effects involve perturbation of solvent on the electronic wave function of the solute held at fixed geometry; indirect effects are due to the relaxation of the solute geometry under the influence of the solvent^{27,28}. The same convention adopted by Witanowski et al.³⁷ was used to describe trends in shielding data; thus, a positive solvent effect indicates an increase in nuclear shielding.

Relative solvent effects are calculated using the corresponding nuclear shielding in cyclohexane as reference. Direct ($\Delta\sigma_{\text{dir}}$) and indirect ($\Delta\sigma_{\text{ind}}$) solvent effects are obtained. Instead of deriving $\Delta\sigma_{\text{ind}}$ from the difference of the PCM-optimised shielding and the PCM shielding of the molecule held at the geometry optimised *in vacuo*, it is obtained from the shielding calculated *in vacuo* for a molecule that has the geometry optimised in solution, thus:

$$\Delta\sigma_{\text{dir}} = \sigma_{\text{sol}}(\text{R}_v) - \sigma_{\text{cyc}}(\text{R}_v) \quad (1)$$

$$\Delta\sigma_{\text{ind}} = \sigma_{\text{vac}}(\text{R}_s) - \sigma_{\text{vac}}(\text{R}_{\text{cyc}}) \quad (2)$$

Where $\sigma_{\text{sol}}(\text{R}_v)$ is the value of the nuclear shielding computed in solution but with the solute in the geometry optimised *in vacuo*, and $\sigma_{\text{vac}}(\text{R}_s)$ is the value of nuclear shielding in vacuo but with the solute geometry optimised in solution. $\sigma_{\text{cyc}}(\text{R}_v)$ and $\sigma_{\text{vac}}(\text{R}_{\text{cyc}})$ are the corresponding parameters for the calculation with cyclohexane.

The atom numbering used for 2-amino-3-mercapto propionamide used in this paper is shown in Fig. 2.

Results and discussion

The calculated total energy, relative energy and dipole moment in going from the gas phase to solution are given in Table 1. By increasing solvent polarity, the total energy and relative energy become more negative, so the stability of the molecule increases. There is an enhancement of the dipole moment on going from the gas phase to the polar medium.

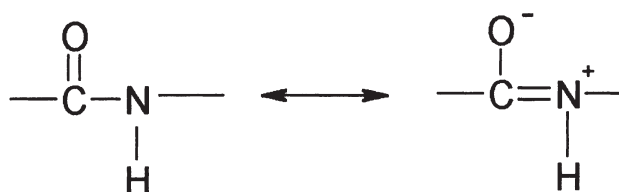


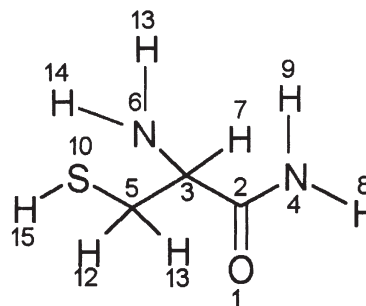
Fig. 1 Partial double bond character of the C–N bond in amides.

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Table 1 Total energies (hartrees) relative energies and dipole moments calculated by PCM model of solvent^a

Solvent	ϵ	E(au)	ΔE^b (kcal/mol)	μ (D)
Vacuo	1	-699.5936337	0	2.9125
Cyclohexane	2.023	-669.6011941	-4.7343	3.2473
CCl ₄	2.228	-699.598344	-2.9496	3.2995
CHCl ₃	4.9	-699.602104	-5.3041	3.5811
THF	7.58	-699.6033241	-6.0681	3.6676
Acetone	20.7	-699.6058666	-7.6602	3.8166
DMSO	46.7	-699.605508	-7.4625	3.8559

^a(HF/6-31++G(2d, p) optimized geometry), ^b($\Delta E = E_{\text{solution}} - E_{\text{vacuo}}$).

**Fig. 2** Atom numbering for 2-amino-3-mercapto propinamide.**Table 2** Optimised geometry in the gas phase and solvent phase^a

Solvent	ϵ	R2-1	R2-4	R4-8	R4-9	A2-4-8	A2-4-9	D1-2-4-8	D1-2-4-9
Vacuo	1	1.19775	1.34418	0.99290	0.99167	118.0128	120.13135	-6.1314	-167.1724
Cyclohexane	2.023	1.20078	1.33985	0.99326	0.99199	118.4433	120.2121	-5.1437	-169.3997
CCl ₄	2.228	1.20117	1.33948	0.99327	0.99221	118.4857	120.2681	-4.9621	-169.9668
CHCl ₃	4.9	1.20376	1.33712	0.99444	0.99266	118.7446	120.2545	-4.3248	-171.3957
THF	7.58	1.20462	1.33614	0.99433	0.99270	118.8536	120.2862	-4.0688	-171.9883
Acetone	20.7	1.20584	1.33537	0.99475	0.99299	118.9468	120.2933	-3.9676	-172.3994
DMSO	46.7	1.20603	1.33477	0.99479	0.99301	119.0003	120.2985	-3.6080	-173.0525

^a(HF/6-31++G(2d, p) optimised geometry)

Table 3 Structural parameters of ground state and TS in the gas phase, CCl₄ and CHCl₃ at HF/6-31G(d) level^a

Parameter	Ground state	TS(gas phase)	TS(CCl ₄)	TS(CHCl ₃)
R21	1.20154	1.18590	1.18732	1.18833
R42	1.34408	1.43635	1.43302	1.43197
R84	0.99368	1.00538	1.00611	1.00665
R94	0.99475	1.00489	1.00548	1.00601
A842	120.453	108.149	108.234	108.222
A942	118.241	107.967	108.144	108.203
D8423	4.0975	-117.632	-118.770	-119.499
D9423	173.291	128.7464	127.555	126.833

^a(TS structures were obtained by STQN method)

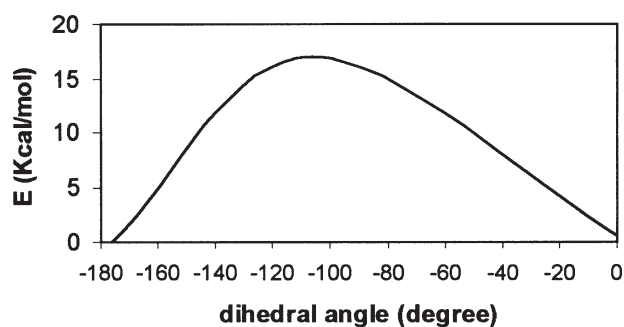
Thus, the interaction between solute and solvent increases and the solute will be more stable than the gas phase.

The calculated changes in structure in going from the gas phase to solution are given in Table 2. The calculated C=O bond length increases, while the C-N bond decreases, with increasing solvent polarity. These changes, lengthening of the C=O bonds and shortening of the C-N bonds, correspond to a small increase in the weight of the dipolar resonance structure (Fig. 1).

Changes in the calculated energy during the C-N bond rotation in the gas phase at the HF/6-31G(d) level, are shown in Fig. 5

Structural parameters of ground state and transition state in the gas phase and two solvents (CCl₄ and CHCl₃) at the HF/6-31G(d) level are given in Table 3. The results in the gas phase by these two methods (C-N bond rotation and STQN) are nearly the same. During the C-N bond rotation, the C-N bond length increases and the C=O bond length decreases. This shows that the π -conjugation in the C-N bond is lost. By increasing the polarity of solvent (CCl₄ to CHCl₃), the C=O bond length in TS increases, whilst the C-N bond length decreases, so the predicted barrier increases.

The predicted barrier in the gas phase increases by increasing the polarity of the solvents. The ground state is more polar than TS in the gas phase and solution (Fig. 8). Thus, the solvent stabilises the ground state more than the TS and then the barrier energy increases. The effect of basis set on the barrier energy (6-31G(d) to 6-31++G) is more than the effect of level of theory (HF to MP2).

**Fig. 5** Variation of Energy during the rotation of dihedral angle (D8432) in the gas phase.

It might be suggested that the optimisation of solute molecules in the solvent followed by shielding calculations is similar to shielding calculations of solvent-solute as an isolated system. However, if the molecule is first optimized in the gas phase and then NMR shielding calculations are performed in the solvent, the solvent-solute interactions are taken into consideration for NMR shielding calculation.

Scrutiny of the data listed in Table 7 reveals that the observed solvent-induced shielding variations are more strongly related to the intensity of the solvent reaction field ($\Delta\sigma_{\text{dir}}$) than to the change of molecular geometry induced by the solvent ($\Delta\sigma_{\text{ind}}$). It can be seen that there is little difference in calculating $\Delta\sigma_{\text{dir}}$ and $\Delta\sigma_{\text{ind}}$ at both HF and B3LYP levels of theory.

Table 7 Calculated values of $\Delta\sigma_{\text{dir}}$ and $\Delta\sigma_{\text{ind}}$ (ppm)

Solvent	ϵ	$\Delta\sigma_{\text{dir}}^{\text{a}}$		$\Delta\sigma_{\text{ind}}^{\text{a}}$		$\Delta\sigma_{\text{dir}}^{\text{b}}$		$\Delta\sigma_{\text{ind}}^{\text{b}}$	
		N4	N6	N4	N6	N4	N6	N4	N6
Cyclohex.	2.023	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CCl ₄	2.228	-0.1678	0.0821	-0.0567	-0.1311	-0.1859	0.0827	0.0532	-0.1426
CHCl ₃	4.9	-1.2031	0.6146	-0.2845	-0.231	-1.3383	0.6198	-0.2179	-0.2349
THF	7.58	-1.558	0.8089	-0.3189	-0.1739	-1.7374	0.8174	-0.2278	-0.1782
Acetone	20.7	-2.0029	1.0637	-0.4279	-0.2337	-2.2422	1.07428	-0.3171	-0.2419
DMSO	46.7	-2.1556	1.1534	-0.4618	-0.2544	-2.4137	1.168	-0.3428	-0.2642

^a(HF/6-31++G(2d, p)//HF/6-31++G(2d, p), ^b(B3LYP/6-31G++(2d, p) //HF/6-31++G(2d, p))

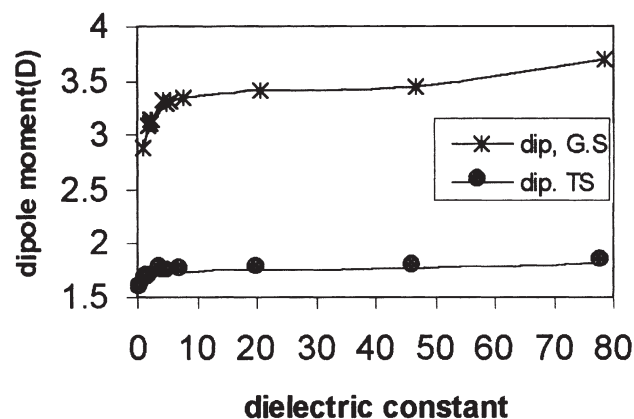


Fig. 8 Calculated dipole moment for ground state and TS at HF/6-31G(d).

This work presents a self consistent reaction field study of rotational barrier energy around the C–N bond and NMR nitrogen shielding calculations for 2-amino-3-mercapto propionamide.

The relative energy and the dipole moment calculated at HF/6-31++G(2d,p) level of theory have a linear relationship with $\ln\epsilon$.

The HF and MP2 levels of theory combined with 6-31G(d) and 6-31++G basis sets predicted that the barrier of rotation in the gas phase increases by increasing the polarity of solvents.

The PCM-CSGT calculations of nitrogen NMR shielding at two levels of theory, *i.e.* HF/6-31++G(2d,p)//HF/6-31++G(2d,p) and HF/6-31++G(2d,p)//B3LYP/6-31++G(2d,p), showed that

the calculated solvent-induced shielding variation is more strongly related to the intensity of solvent reaction field rather than to the change of molecular geometry induced by the solvent.

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