Reactivity of Planar and Twisted Amides in Vacuum and Aqueous Environments: an *ab initio* MEP Study

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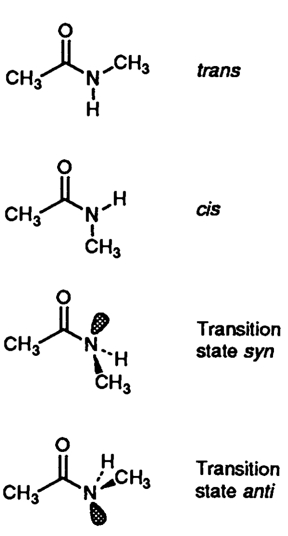
We present an *ab initio* study on the amide resonance *in vacuo* and water environments. The planar *cis* and *trans* minima, as well as the *syn* and *anti* twisted conformations of *N*-methylacetamide (NMA) were fully optimized at the 6-31G* level. *Ab initio* 6-31G* wavefunctions obtained from *in vacuo* and self-consistent reaction field calculations were used to compute the corresponding molecular electrostatic potentials for the four conformations of NMA in gas phase and water. Finally, MEP difference maps, and electrostatic charges were used to study the changes in the charge distribution occurring when the NMA molecule interacts with a hydride molecule placed in the surroundings of the amide hydrogen.

The amide bond is one of the most important chemical structures, which among other factors is responsible for the primary structure of proteins. A proper representation of its chemical characteristics is essential to explain the chemical and biochemical properties of large molecules, such as proteins. The structure and reactivity of the amide bond has been mainly explained from the concept of chemical resonance, as it was suggested in the 40's by L. Pauling.[1] Accordingly, the existence of a partial π character for the C–N bond is suggested, which is due to the transfer of electrons from the nitrogen to the carbonyl oxygen. From this scheme, a large number of molecular properties of amides, such as their planarity, IR C=O frequencies, and the short length of the bond N–C(O) have been explained. Recently, an alternative model for the amide resonance has been suggested[2–4] from *ab initio* calculations *in vacuo* and Bader's charge analysis.[5] According to this model, the electron transfer in planar amides appears to occur not in the direction N→C, but in the direction C→N.

Relevant differences in the reactivity of amides are derived from these two models. When the amide bond is rotated, and consequently resonance is broken, an increase in the electrophilicity of the carbonyl carbon, and in the nucleophilicity of the nitrogen is predicted from Pauling's scheme. Nevertheless, the reverse situation is expected according to the other resonance scheme. In fact, inspection of atomic charges derived from Bader's analysis show no change in the charge of the oxygen, an increase in the electron density in the carbon, and a loss of electrons in the nitrogen. However, it is not easy to predict changes in nucleophilicity/electrophilicity from these changes in the atomic charges, since dipoles and higher order multipole terms must be used in addition to Bader's charges to obtain a suitable picture of the molecular electrostatic properties. Furthermore, the determination of the magnitude of such changes in environments other than gas phase, and particularly in aqueous solution, is very interesting to gain insight into the reactivity of amide structures.[6]



Scheme 1

In this paper, we present a wide study on the electrostatic properties of *N*-methylacetamide (NMA), a model for the peptidic bond. The study was performed considering not only the two planar conformations of NMA (*cis* and *trans*), but also the *anti* (TS_{anti}) and *syn* (TS_{syn}) transition states corresponding to the *cis*↔*trans* isomerization (see Scheme 1). For all the conformations, we have computed the electrostatic properties of the molecules in both gas phase and water solution. We have also explored the different ways in which planar and twisted amides accommodate perturbations resulting from the introduction of a negative charge in their surroundings.

Methods

Ground state molecular geometries were fully optimized at the *ab initio* 6-31G* level, since geometrical and electronic properties of amides in both gas phase and solution[3,7–11] are well reproduced at this computational level. The use of larger basis sets or even the inclusion of electron correlation is expected to lead to very small variations in the molecular electrostatic distribution.[12] For all the conformations, frequency analysis was performed to verify the minimum-energy structure of the *cis* and *trans* conformations, as well as the transition state character of the TS_{anti} and TS_{syn} conformers (Scheme 1).

The molecular electrostatic potential (MEP) was computed at the *ab initio* 6-31G* level in several planes: the carbonyl plane, and the planes at 2 and 4 Å above and below the carbonyl plane. Indeed, additional MEP maps available upon request to the authors are: (*a*) the plane defined by C(O), N, and the nitrogen MEP minimum; and (*b*) the plane normal to the carbonyl plane passing through the C–O bond.

MEP minima were located with an error less than 0.01 kcal mol^{-1},* by using a gradient method,[13] and used to define several reactivity lines, where the MEP was also computed: the lines defined by the vectors O(nuclei)→O(MEP minimum) and N(nuclei)→N(MEP minimum), and the line perpendicular to the carbonyl plane passing through the carbonyl carbon.

Finally, the study of the MEP distribution for the unperturbed NMA was complemented with the analysis of the effect that the introduction of a negative charge in the surroundings of the NMA has on the electrostatic distribution. This analysis was performed by using two different approaches: (i) to compute the MEP differences due to the effect of the hydride anion; and (ii) to compute the electrostatic charges for the complex. The first test provides qualitative, but detailed information of the effect of the hydride on the whole MEP distribution, whereas the second gives average, but quantitative information about such an effect. Calculations of the NMA ··· H^- complexes were performed by using the unperturbed NMA optimized geometry.† The hydride ion was placed colinear to the N–H bond at 2, 3 and 4 Å from the hydrogen.

MEP differences were computed by using eqn. (1), which takes advantage of the use of common internal geometry for monomers and complexes. Electrostatic charges centred at the nuclei were determined from the fitting between coulombic and quantum mechanical MEPs computed in two layers placed at 1.4 and 1.8 times the van der Waals radii of the atoms. A density of 10 points Å^{-2} was used to ensure the statistical quality of the charge distribution. Previous studies showed that statistical errors less than 0.001 e$^-$ in the charges are expected following this fitting procedure.[11,14]

$$\Delta\mathrm{MEP} = \mathrm{MEP}^{\mathrm{NMA-H}} - \mathrm{MEP}^{\mathrm{NMA}} - \mathrm{MEP}^{\mathrm{H}} \quad (1)$$

Computations *in vacuo* were complemented with calculations in which the effect of water on the electrostatic properties was included by means of Tomasi's SCRF algorithm,[15,16] which has provided excellent estimates of solvation free energies of different amides.[11,17] This sophisticated algorithm, which is described in detail elsewhere,[15,16] describes the solvent as a continuum dielectric characterized by suitable macroscopic properties, such as the permittivity. The major advantages of the algorithm with regard to other continuum models are: (i) the use of a rigorous expression for the solute–solvent electrostatic interaction; and (ii) the use of molecular-shaped solute cavities. Calculations in aqueous solution were performed at a temperature of 298 K by using a dielectric constant of 78.5. The molecular cavity was built following the algorithm of Pascual Ahuir *et al.*[18] considering a cavity size equal to 1.2 times the van der Waals radii of atoms. In our previous calculations,[11] such cavities represented the first 'hydration charge' shell and provided good estimates of ΔG of solvation for NMA.

Geometry optimization and solvation calculations were performed by using locally modified versions of HONDO77[19] and MONSTERGAUSS[20] computer programs. MEPs and electrostatic charges were obtained by using MOPETE/MOPFIT computer programs.[21] All the calculations were performed on the IBM-3090 computer at the Centre de Supercomputació de Catalunya (CESCA).

Results and Discussion

MEPs in gas phase and in aqueous solution of the four conformers were computed in several planes. Even though the carbonyl plane is the most informative, especially about the attack of a positive charge, planes above and below the carbonyl moiety should be studied to gain insight into the reactive characteristics in front of the attack of a negative charge.[22] For this purpose, and following the strategy suggested by Pullman[23,24] and used by ourselves in other studies,[25] MEPs at 2 and 4 Å above and below the carbonyl plane were also evaluated. Fig. 1 shows the *in vacuo* MEP maps in the carbonyl plane, whereas the *in vacuo* 'out of the plane' MEP maps at 2 Å are displayed in Fig. 2.‡ The MEP minima in gas phase and in aqueous solution are shown in Table 1.

MEPS in the carbonyl plane (Fig. 1) of *trans*, *cis* and TS_{syn} can be divided in two different areas: a positive region due to the proximity of the methyl groups; and a negative region originated from the oxygen lone pairs (*cis*, *trans*), and oxygen and nitrogen lone pairs (TS_{syn}). The TS_{anti} conformation shows two negative regions of MEP (corresponding to the nitrogen and oxygen lone pairs), which are placed in opposite regions of the molecule. This electrostatic distribution explains the small dipole of the TS_{anti} conformation (1.8 D), in contrast with the dipole moment (3.9–4.2 D) of the other conformers.

Inspection of MEP maps in the carbonyl plane, and of the numerical results in Table 1, clearly shows the large effect that the twisting of the amide bond has on the electrostatic properties of NMA. The most relevant differences between planar and twisted conformations are found in the nitrogen area, where a large negative region appears in twisted conformations, and in the oxygen, where the depth (in absolute value) of the MEP minima corresponding to the lone pairs (especially that located in the *C*-side) decreases when the amide is twisted, this effect being particularly remarkable for the TS_{anti} conformation.

The topology of the MEP in the oxygen area is quite similar for *cis* and *trans* conformations, but the energy of the MEP minima is slightly different (see Table 1), indicating a larger nucleophilicity for the *cis* conformer. In contrast, large differences appear when the two transition states are compared. Thus, the MEP topology around the oxygen for TS_{anti} is very similar to that of *cis* and *trans* conformers, even though the well depth is smaller. However, the TS_{syn} shows a complex topology due to the proximity of the nitrogen lone pair. This is reflected in the MEP minima (Table 1), since *C*-side and *N*-side minima differ around 8 kcal mol^{-1} for TS_{syn}, in contrast with the range of -2 to -4 kcal mol^{-1} for the remaining conformers.

The 'out of plane' maps (Fig. 2) show a common profile, with a negative region over the oxygen, and a positive region on the methyl groups. As expected, the nucleophilicity in the oxygen area decreases as the distance from the carbonyl plane increases. Nevertheless, even at 4 Å a negative region appears over the oxygen, it being due to (i) the π electron distribution of the oxygen; and (ii) an 'out of the plane' component of the oxygen lone pairs. Oxygens in planar structures are better nucleophiles than those in twisted conformers also for 'out of the plane' electrophilic attacks. Nevertheless, the differences become smaller as the MEP is computed in planes more distant from the molecule.

The nitrogen of the planar structures appears as a poor electrophile at 4 Å, and changes to a poor nucleophile at 2 Å, which reflects the presence of a small π MEP minima (Table 1). The situation is very different for twisted structures, since the 'out of the plane' MEP in the nitrogen region is dominated by the nuclear repulsion term of the hydrogen and the methyl group. These plots reflect the difficulties for an 'out of the plane' attack of an electrophile to the nitrogen of twisted conformations. The nitrogen lone pair of twisted structures is placed in the carbonyl plane, and its 'out of the plane' component is very

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* 1 kcal mol^{-1} = 4.18 kJ mol^{-1}.

† The use of a common geometry for perturbed and unperturbed NMA is required for the calculation of the MEP difference maps.

‡ Figures not explicitly shown are available upon request from the authors.

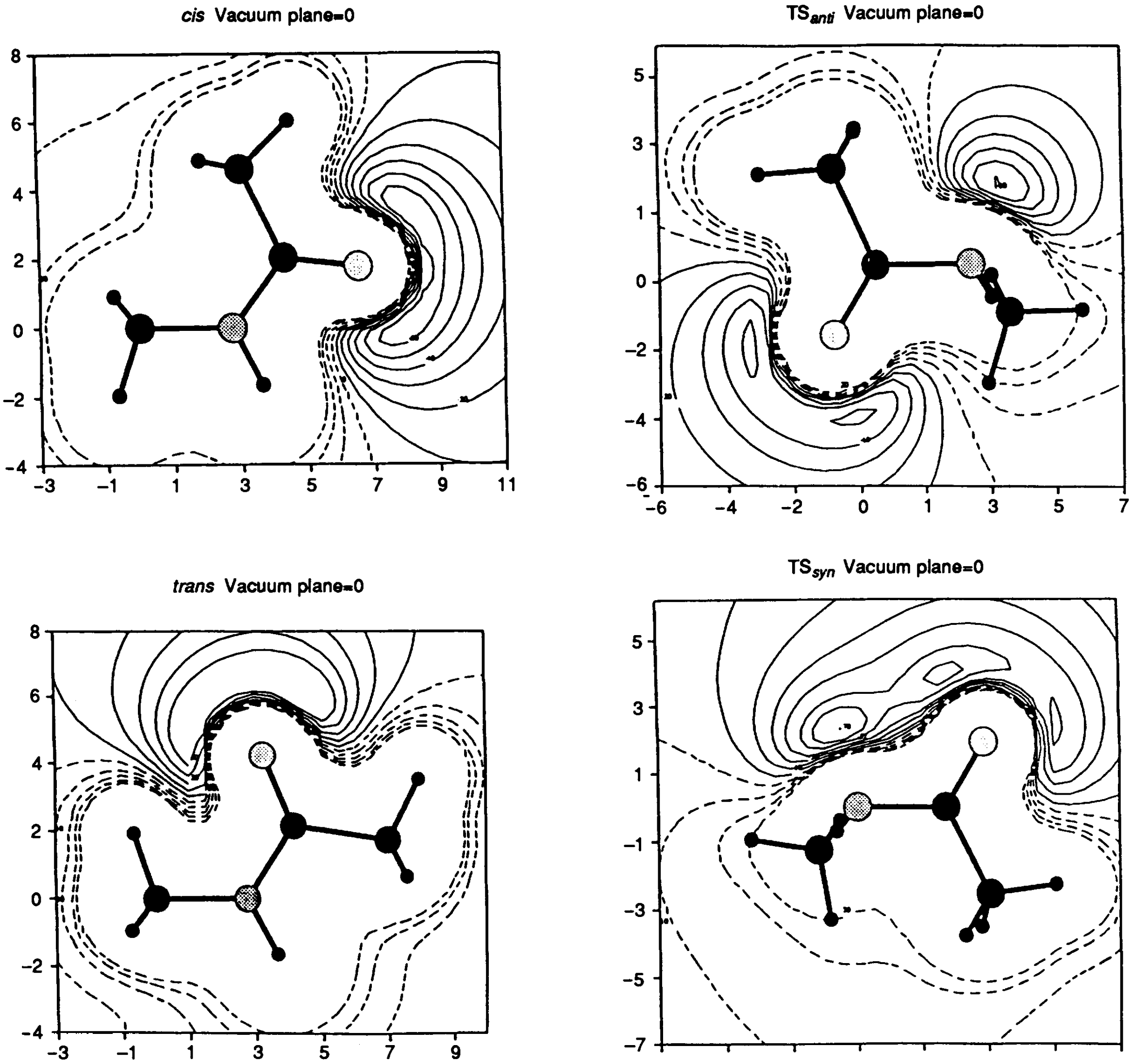

Fig. 1 MEP maps *in vacuo* for the four conformations of NMA in the carbonyl plane. Isopotential lines are in kcal mol^{-1} and coordinates are in atomic units.

Table 1 Energy (in kcal/mol) of the MEP minimum originated from lone pairs of nitrogen (N–LP) and oxygen [O–LP(C), *C*-side; O–LP(N), *N*-side] for the four conformations of NMA *in vacuo* and in aq. solution. Values in solution are given in parentheses

	cis	*trans*	TS_{anti}	TS_{syn}
N–LP	−12.92 (−11.09)	−11.26 (−7.52)	−61.69 (−62.93)	−70.36 (−80.55)
O–LP(C)	−69.64 (−89.45)	−68.58 (−88.17)	−54.16 (−66.80)	−54.84 (−70.24)
O–LP(N)	−67.06 (−86.74)	−63.98 (−82.92)	−51.98 (−64.19)	−63.22 (−81.13)

small, especially for the TS_{anti}, in contrast to the behaviour of the oxygen lone pairs.

The carbonyl carbon is placed in an almost neutral region surrounded by negative (O and N) and positive (CH_3) regions for planar conformations, but it appears in a clear positive region surrounded by large positive areas (CH_3 or H), and a negative region (O), indicating an increase in the carbon electrophilicity when the amide is twisted. In this respect, steric considerations suggest the *H*-side of the carbonyl group for twisted structures to be the preferred route for the attack of a nucleophile, but no significant difference exists in terms of electrostatic interaction between the two carbonyl sides of twisted conformations.

The effect of water on the electrostatic distribution was analysed from the comparison of the MEP in the carbonyl plane (Fig. 3) and 'out of the plane' maps with regard to the *in vacuo* MEP maps. Indeed, MEP minima in aqueous solution are displayed in Table 1. Results demonstrate the great effect of water on the electrostatic distribution of NMA, which leads to a larger charge separation in all the structures (the dipole moment increases 25–30% according to previous calculations[11]). Thus, the negative region around the oxygen becomes more negative (note the increase of 25% of the MEP minima depth), and the positive region surrounding the methyl groups become more positive (a migration of isopotential lines +10 and +20 to outer regions is observed). Other local effects of water are especially noticeable. Thus, the nitrogen nucleophilicity of the TS_{syn} increases in water around 14%, but no change is detected for the TS_{anti}, and even a small decrease in the π MEP minima is detected for planar structures. Finally, the carbonyl carbon

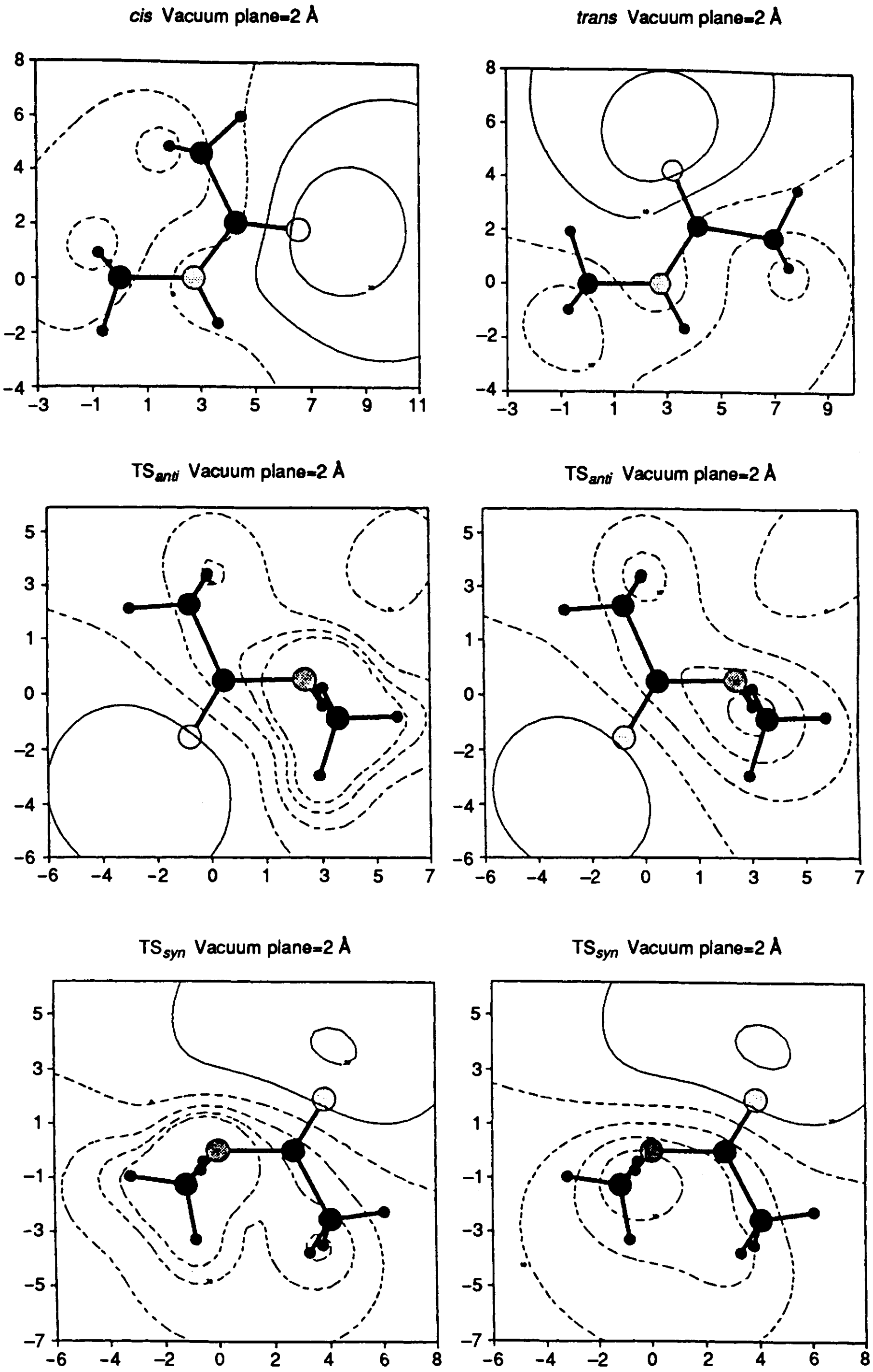

Fig. 2 MEP maps *in vacuo* for the four conformations of NMA in the plane at 2 Å above (*H*-side), and below (CH_3-side) the carbonyl plane. Isopotential lines are in kcal mol^{-1}, and coordinates are in atomic units.

electrophilicity remains almost unaltered by the presence of water.

The analysis of the different MEP planes provides wide and useful information about the electrostatic distribution around the molecule, but it has an obvious qualitative nature. Hence, we also computed the MEP in the most relevant pathways for the attack of an electrophile: N→N(MEP minimum), O→O(MEP minimum *C*-side), and O→O(MEP minimum *N*-side), and for the attack of a nucleophile: the line perpendicular to the carbonyl plane passing through the carbonyl carbon [line C(O)–X]. The graphical representation of the results is displayed in Fig. 4.

Results show the larger nucleophilic character of the nitrogen in twisted amides in both gas phase and solution with regard to planar conformations. In fact, the nitrogen is an electrophile at 1.6 times the van der Waals radii of the nitrogen (a typical distance for non-bonded interactions) for planar conformations, but it becomes a good (TS_{anti}) or excellent (TS_{syn}) nucleophile when the amide bond is twisted. This result agrees with the electron flow N→C in planar structures suggested by Pauling's resonance model. It is also noticeable the larger nucleophilicity of the TS_{syn} with regard to the TS_{anti}, which can be understood from the proximity between nitrogen and oxygen lone pairs for the TS_{syn}. Comparison of results *in vacuo* and in solution confirms the general trends noted for the analysis of MEPs maps: (i) the small effect of solvation in the TS_{anti}; (ii) the not-

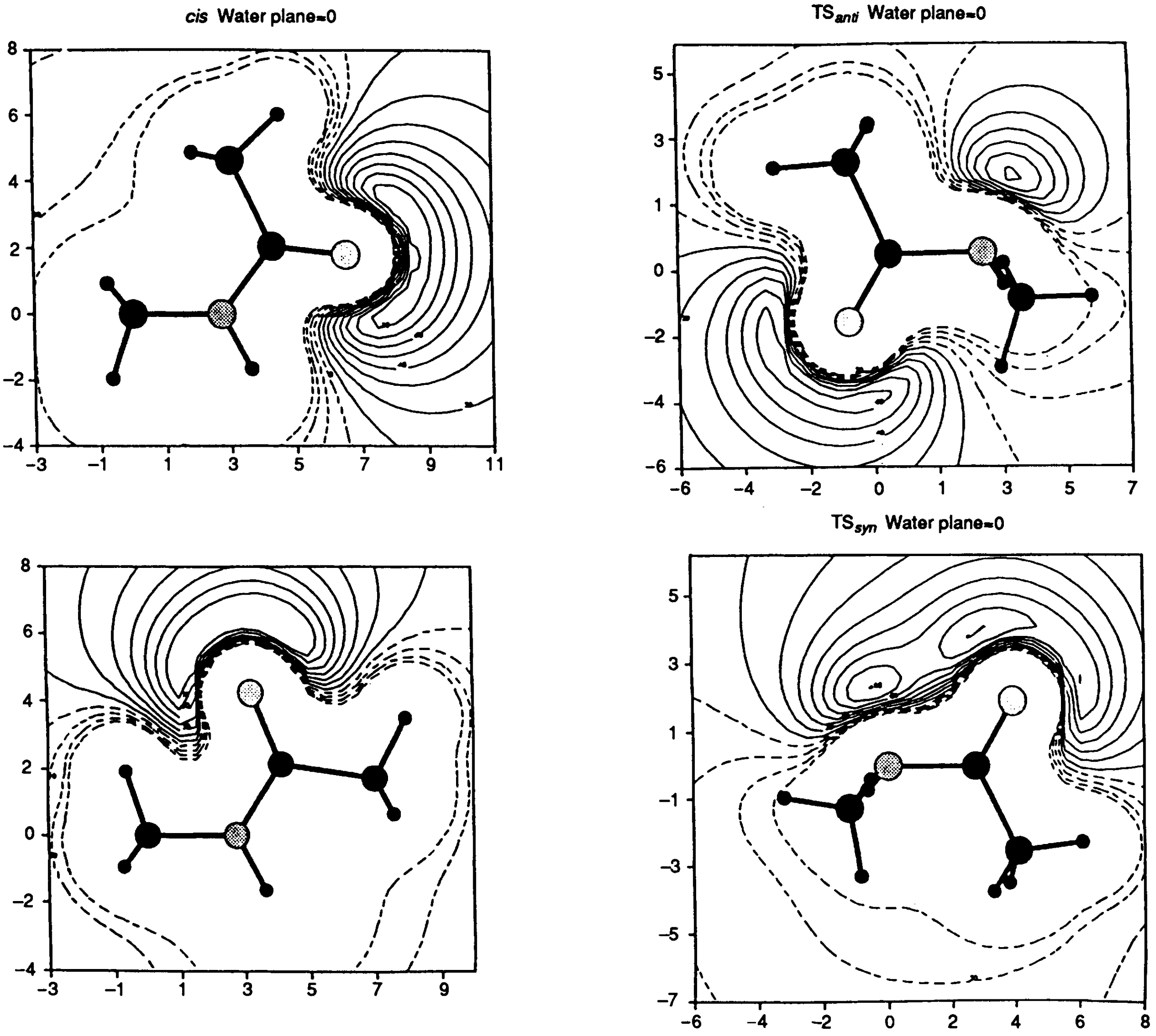

Fig. 3 MEP maps in aqueous solution for the four conformations of NMA in the carbonyl plane. Isopotential lines are in kcal mol^{-1}, and coordinates are in atomic units.

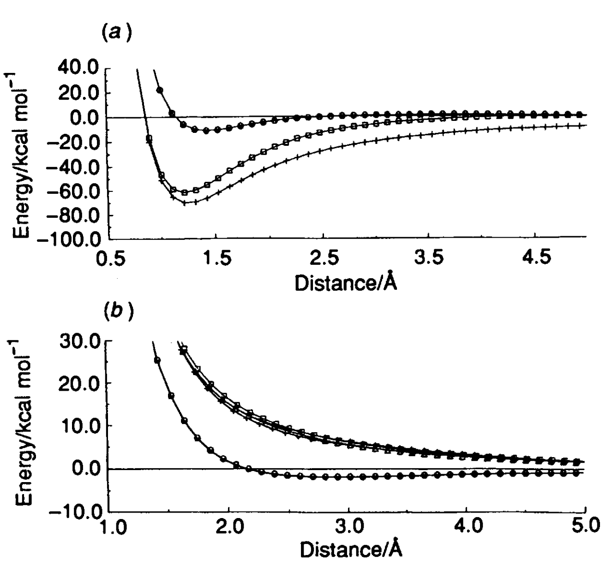

Fig. 4 MEP (*a*) in the line N→N(MEP minimum); and (*b*) in the line perpendicular to the carbonyl plane passing through the carbon atom, for the four conformations of NMA *in vacuo*. Values are in kcal mol^{-1}. (*a*): O, *cis*; ×, *trans*; □, TS_{anti}; +, TS_{syn}. (*b*): ○, *cis*; ×, *trans*; □, TS_{anti} *C*-side; TS_{anti} *H*-side; △, TS_{syn} *H*-side; *, TS_{syn} *C*-side.

able increase of the nucleophilicity for the nitrogen in the TS_{syn}; and (iii) the slight decrease in the nucleophilicity in planar conformations.

MEPs in the line C(O)–X for the different conformers (Fig. 4) shows the larger electrophilicity of the carbonyl carbon in twisted forms with respect to planar conformations. In fact, the carbonyl carbon of planar conformers is a poor electrophile, since at 1.6 times the van der Waals radii of the carbon the MEP takes negative values. In contrast, twisted structures show positive MEP values in both sides of the molecular plane. This increase in the electrophilic character of the C(O) agrees with Pauling's model. Fig. 4 confirms the two effects previously described: (i) there is no clear electrostatic preference for either side of the molecule for a nucleophilic attack to C(O); (ii) both transition states exhibit a similar electrophilicity at the C(O). Comparison of results *in vacuo* and in solution indicates that water has a small effect on the electrophilicity of C(O). This agrees with the Monte-Carlo based suggestion that the increase in the energetic barrier associated to the attack of a nucleophile (like OH^-) to a carbonyl centre[26] in water is not due to an intrinsic change in the reactivity of the carbonyl carbon by the solvent, but to a dynamical effect due to the breaking of the solvation layers of both nucleophile and electrophile during the reaction.

The shape of the MEP profiles in the lines O–LP(N) and O–LP(C) are very similar to that found for the line N→N(MEP minimum). As expected, a clear minimum at around 1.1 Å from the oxygen appears for all the conformations. Such minima are deeper for planar structures than for twisted ones (see Table 1), even though the MEP minimum (*N*-side) depth for TS_{syn} is similar to those of planar conformations. The nucleophilicity decreases in all cases as the distance from the oxygen increases, but such a decrease seems to be slightly faster for the planar conformations. Thus, if a typical interaction distance of 1.6 times the van der Waals radii of the oxygen is considered, the TS_{syn} exhibits MEP values smaller than those of the planar conformers: *cis* −25 kcal mol^{-1}, *trans* −23 kcal mol^{-1}, TS_{syn} −30 kcal mol^{-1}, and TS_{anti} −18 kcal mol^{-1} when looking at the line O–LP(N), whereas the *cis* exhibits the deepest MEP value in the line O–LP(C), although differences with respect to the other conformers are small: *cis* −27 kcal mol^{-1}, *trans* −26 kcal mol^{-1}, TS_{syn} −22 kcal mol^{-1}, and TS_{anti} −20 kcal mol^{-1}. If the MEP values in both lines at 1.6 times the van der Waals radii are added to estimate the nucleophilic characteristics in the outer regions, we obtain the following ordering: $\mathrm{TS}_{syn} \approx cis \leqslant trans < TS_{anti}$, which agrees with previous charge analysis,[11] where charges at the oxygen for planar and TS_{syn} were similar, the negative charge for the TS_{anti} being clearly smaller (in absolute value).

According to Pauling's model, the nucleophilicity of the oxygen should decrease when the amide bond is twisted. Such an effect appears in TS_{anti}, but it is not observed in TS_{syn}. This different behaviour can be realised bearing in mind the 'cooperative' effect of nitrogen and oxygen lone pairs in TS_{syn}. Accordingly, present results support that the electron flow in planar structures in the direction N→C is at least partly propagated to the oxygen, which leads to an increase in the oxygen nucleophilicity for planar amides. The extent of such an electron flow, and consequently the implication of the oxygen in the resonance, remains to be elucidated. Nevertheless, the small, but not negligible change in the C–O bond length occurring when the amide is twisted (in our 6-31G* calculations the bond is enlarged from 0.012 to 0.015 Å), our previous charge analysis,[11] and the moderate change in the nucleophilicity of the oxygen when the amide is twisted seems to support a real implication of the oxygen in the amide resonance, although such an implication is probably not as large as usually suggested by most textbooks.

Water leads to a larger increase of the well depth (around 7 kcal mol^{-1}) for planar structures than for twisted conformers, which enlarges the difference in the nucleophilicity of the oxygen between planar and twisted conformations. The effect of water decreases as the distance from the oxygen increases, but, even at distances of 1.6 times the van der Waals radii of the oxygen, a non-negligible increase in the nucleophilicity of the oxygen around 8 kcal mol^{-1} is found. It is worth noting the effect of water on the MEP in the line O–LP(N). Thus, the *cis* conformer has the deepest minima *in vacuo* at 1.5 Å, but the TS_{syn} exhibits the most negative values (up to 5–10 kcal mol^{-1}) at larger distances. In contrast, *cis* and TS_{syn} conformations show similar MEP values in aqueous solution for distances greater than 2 Å, which indicates the larger effect of water on the increase in the nucleophilicity of the oxygens for planar amides.

Present results support Pauling's resonance scheme. Nevertheless, in order to confirm the suitability of the model to explain the reactivity of amides, we also determined the changes on the electrostatic properties when the electronic distribution of NMA was perturbed by a charged group. Particularly, a hydride anion was placed colinear to the N–H bond at 2, 3 and 4 Å from the hydrogen. The hardness of the hydride ion, its location at a reasonable distance from the resonance system, and its indirect interaction (*via* the N–H bond) with the resonance system guarantee the introduction of a small perturbation in the system, which is not able by itself to change the resonant scheme of the amide. Such a perturbative effect was studied in two different ways: (i) the MEP differences between the NMA–H^- and its constituents were computed as noted in eqn. (1); and (ii) the electrostatic charges computed and integrated over the *C*- and *N*-sides of the amide bond. Combination of both tests provides a good insight into the changes in the electronic distribution of NMA due to the presence of the hydride molecule.

MEP difference maps corresponding to the four conformations with the hydride at 2 Å are shown in Fig. 5, which shows all the regions where the variation of the electrostatic interaction between the complex and the monomer was greater than 15 kcal mol^{-1}. MEP difference maps with the hydride at 3 and 4 Å are qualitatively similar, but the magnitude of the effects is smaller.

Results show the negative charge migration from the hydride to NMA. The charge is not transferred to the amido hydrogen, which becomes more electropositive, but it moves to the nitrogen, and to the rest of the molecule. The increase of the positive charge on the hydrogen and of the negative charge on the nitrogen reinforces the local dipole along the bond N–H, which will then interact more favourably with the hydride. The charge transfer from the hydride to NMA exhibits different trends between *cis* and *trans* conformations. The *cis* mainly accumulates charge on the carbonyl carbon and the methyl groups, but the charge is mainly located on the oxygen for the *trans* conformation. This different behaviour is easily understood bearing in mind the strong electronic repulsion in the *cis* conformer due to the proximity of the oxygen to the hydride, this effect being not present in the *trans* conformation. A detailed inspection of plot (*a*) indicates that the migration along the C=O bond largely occurs *via* the π bond, as expected from Pauling's resonance model.

The charge redistribution in twisted structures is similar to that of planar conformations, but the charge transfer to the carbon side is smaller, since the π C–N bond is broken, and consequently the charge mainly remains on the *N*-side of the amide bond. It is interesting to note that the charge migration *via* σ bond to the carbonyl carbon partly affects to the oxygen in the TS_{syn} conformation, but this effect is impeded by the presence of the hydride in the TS_{anti}. Note also that the charge transferred to the oxygen is clearly smaller for the TS_{syn} than for the *trans* conformation, since the amount of charge migrated to the carbonyl atom is smaller in the case of the twisted structures.

The complexity of the MEP distribution resulting from the introduction of the hydride anion makes it difficult to obtain reliable electrostatic charges, since the MEP in the surroundings of the nuclei will suffer a large anisotropy. Nevertheless, useful information about the electron migration along the C–N bond can be obtained if charges at both sides of the amide bond are integrated.[4,11] Two integrated sets of charges were evaluated for the different complexes: the ΣQ_N, which is equal to the addition of the charges on nitrogen, amide hydrogen and *N*-methyl, and ΣQ_C, which results from the addition of the charges on carbonyl carbon, oxygen, and *C*-methyl. Moreover, the difference between ΣQ_C and ΣQ_N (GRD), which measures the charge gradient along the C–N bond, and the total charge transferred ($Qt = \Sigma Q_C + \Sigma Q_N$) were also computed to gain insight into the magnitude of the perturbative effect introduced by the hydride anion. All these parameters, which are reported in Table 2, were compared to those obtained for the NMA alone.

Integrated charges for the unperturbed NMA (first row in Table 2) show the large difference in the charge distribution along the C–N peptidic bond. Thus, comparison of charge gradient for planar (0.15 e) and twisted structures (0.55 e) evidences the flow of electrons in the direction C→N when the amide bond is twisted. This result agrees with the changes in nucleophilicity and electrophilicity upon the twisting discussed previously.

Results in Table 2 provide an average estimation of the

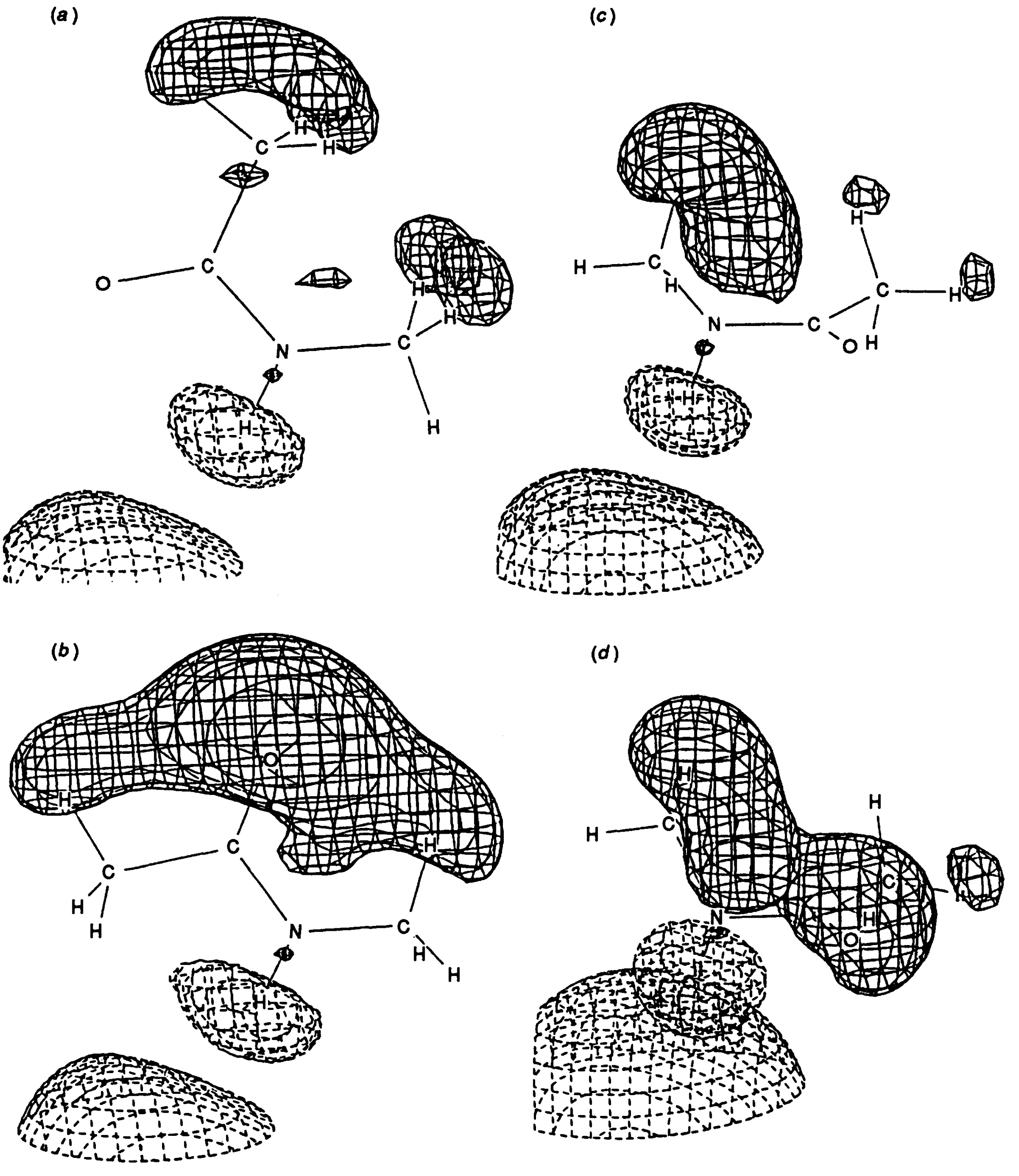

Fig. 5 3-D MEP difference maps for the complex between a hydride ion and NMA (*a*) *cis*, (*b*) *trans*, (*c*) TS_{anti}, and (*d*) TS_{syn}. The hydride is placed at 2 Å from the H(N) atom. Solid contours mean positive difference values, whereas dotted contours mean negative values [see eqn. (1)]. Plots show only the areas where a variation greater (in absolute value) than 15 kcal mol^{-1} in the MEP occurs.

charge redistribution originated from the perturbative effect of the hydride. Obviously, the closer the hydride, the larger the charge transfer (see Qt in Table 2). Thus, only few hundredths of electron are transferred when the hydride is placed at 4 Å, but around 0.18 electrons are transferred at 2 Å. Even though planar conformations have a slightly larger ability to acquire negative charge than twisted conformations, the difference is small. Therefore, the perturbative effect depends more on the nature of the hydride than on the electronic structure of the NMA. Nevertheless, the distribution of the transferred charge is different in planar and twisted amides. Thus, planar conformations accommodate charge mainly in the *C*-side of the peptidic bond, whereas the *N*-side is the preferred position for twisted conformations. As a result, the charge gradient along the C–N bond decreases when introducing the hydride anion for planar conformations, but increases for twisted structures. The fact that most of the 'extra' charge is accommodated in the *N*-side of the peptidic bond in twisted structures can be understood bearing in mind that the π-conjugation is broken, and accordingly the electron transfer is strongly hindered. In contrast, when planar structures are considered, the 'extra' charge flows in the direction N→C.

As a summary, results *in vacuo* and in solution presented in this paper provide a reliable picture of the changes in the nucleophilic and electrophilic properties of NMA when the amide bond is twisted. Assuming that an increase in the electrostatic nucleophilicity (electrophilicity) of an atom can be related to an increase in its negative (positive) charge, and due to the rigorous definition of the MEP, the analysis of the molecular electrostatic distribution is expected to provide information about the nature of the amide resonance without the uncertainties intrinsic to any charge analysis.

Table 2 Integrated set of the electrostatic charges evaluated for the complexes NMA–H$^-$ (see text for more details)[a]

		cis	*trans*	TS_{anti}	TS_{syn}
NMA	ΣQc	0.088	0.069	0.279	0.272
	ΔΣQc	0.000	0.000	0.000	0.000
	ΣQn	−0.088	−0.069	−0.279	−0.272
	ΔΣQn	0.000	0.000	0.000	0.000
	GRD	0.176	0.138	0.558	0.544
	ΔGRD	0.000	0.000	0.000	0.000
	Qt	0.000	0.000	0.000	0.000
NMA···H$^-$ (4 Å)	ΣQc	0.058	0.033	0.268	0.261
	ΔΣQc	−0.030	−0.037	−0.010	−0.011
	ΣQn	−0.074	−0.048	−0.280	−0.274
	ΔΣQn	0.014	0.022	−0.002	−0.002
	GRD	0.132	0.081	0.548	0.535
	ΔGRD	−0.044	−0.057	−0.010	−0.009
	Qt	−0.016	−0.015	−0.012	−0.013
NMA···H$^-$ (3 Å)	ΣQc	0.007	−0.023	0.253	0.241
	ΔΣQc	−0.081	−0.092	−0.026	−0.031
	ΣQn	−0.085	−0.061	−0.326	−0.318
	ΔΣQn	0.003	0.008	−0.047	−0.046
	GRD	0.092	0.038	0.579	0.559
	ΔGRD	−0.084	−0.100	0.021	0.015
	Qt	−0.078	−0.084	−0.073	−0.077
NMA···H$^-$ (2 Å)	ΣQc	−0.037	−0.074	0.224	0.200
	ΔΣQc	−0.127	−0.143	−0.055	−0.072
	ΣQn	−0.146	−0.114	−0.396	−0.379
	ΔΣQn	−0.058	−0.045	−0.117	−0.107
	GRD	0.109	0.040	0.620	0.579
	ΔGRD	−0.067	−0.098	0.062	0.035
	Qt	−0.183	−0.188	−0.172	−0.178

[a] ΣQ_C is the addition of charges on carbonyl carbon, oxygen and *C*-Me. ΣQ_N is the addition of charges on nitrogen, amide hydrogen and *N*-Me. $\Delta\Sigma Q_C$ and $\Delta\Sigma Q_N$ are differences between integrated sets of charges for NMA–H$^-$ with regard to the unperturbed NMA. GRD is the difference between ΣQ_C and ΣQ_N, and ΔGRD is the difference with regard to the unperturbed NMA. Qt is the charge transferred from the hydride to NMA.

The MEP of the different conformations of the NMA, as well as the analysis of the perturbative effect of a hydride molecule, reflects an electron flow when the amide bond is twisted consistent with the classical Pauling's mechanism, although the implication of the oxygen in the mechanism is perhaps not as large as it is usually assumed. Additional work is necessary to understand in detail the fine nature of the resonance effect. Nevertheless, present results, which agree with other previous theoretical calculations,[11,27–29] and a large number of experimental evidences[30,31] reinforces the validity of that model to explain amide structure and reactivity.

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