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Ab initio study of tautomerism and hydrogen bonding of β-carbonylamine in the gas phase and in water solution

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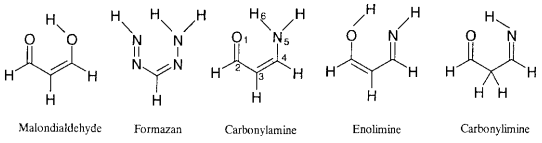
Abstract. All the possible conformations of the three tautomeric isomers of simple β-carbonylamine were fully optimized at ab initio MP2/6-31G** and B3LYP/6-31G** levels in order to determine the conformational equilibrium and the energies of the O—H···N and O···H—N hydrogen bridges. For the most interesting conformations, further calculations in water solution were also carried out. It was found that carbonylamine is the most stable tautomer, followed by enolimine and carbonylimine. This order of stability does not change in solution. O—H···N is the strongest hydrogen bridge, but in solution its energy as well as that of the O···H—N one are dramatically lowered. The deprotonation energy was also calculated and discussed.

Key words: Carbonylamine – Hydrogen bonding in the gas phase and in water solution

1 Introduction

Homo- and heteronuclear hydrogen bonds involving oxygen and/or nitrogen atoms are very interesting systems because they are present in numerous biological molecules and can give rise to very strong intramolecular hydrogen bridges when assisted by resonance. Their importance in chemistry and biology is mainly due to the capital role played in determining the equilibrium conformation of all biological macromolecules as proteins, polysaccharides, barbiturates, etc. [1, 2]. Among the intramolecular bridges, the O—H···O one of malondialdehyde (MDA) has been widely studied from experimental as well as from theoretical points of view both for the parent and for numerous derivatives [3–8, and Refs. therein]. Detailed information concerning the hydrogen bonds involving the nitrogen atom are by far of lower quantity and quantitative estimates of their strengths are seldom available. The N—H···N bridge of formazan (FMZ) has recently been studied by the present authors [9] and it was found to be weaker than the O—H···O one; its energy, also estimated by using rotational barriers, should be in the range of about 30 kJ/mol. Quantitative energetic data are also lacking for the N—H···O (predominant in fibrous and globular proteins) and O—H···N (predominant in nucleoside and nucleotide crystal structures) bridges. Detailed information concerning intramolecular N—H···O and O—H···N hydrogen bonds can be obtained from theoretical studies of carbonylamines (CA).

CA are Schiff-base derivatives of β-dicarbonyls; they can be considered as intermediate molecules between MDA and FMZ and would exist in three tautomeric forms, as shown in Scheme 1.



In contrast to MDA and FMZ, where the proton-transfer process gives rise to equivalent isomers, here, if it occurs, it should produce the enolimine (EI) tautomer, the geometry and stability of which are different from CA. Some reports on thermochemical [10] and crystallographic [11] studies of β-carbonylamine derivatives and IR [12–15] and NMR [16] spectral studies on the tautomerism of these compounds are available in the literature. Such findings indicated the possibility of a tautomeric equilibrium between CA and EI [13, 14], the former being the most stable tautomer, whilst the latter, on grounds of acid dissociation constants in aqueous dioxan, is of major importance in solution [17]. The carbonylimine (CI) tautomer would be the least stable and its presence was excluded because no absorption was observed in the 1700 cm^{-1} IR region, typical of a free carbonyl group [13, 14]. As far as experimental quantitative estimates concerning the O—H···N and N—H···O hydrogen-bridge energies are concerned, in the literature a value of 40.6 kJ/mol ($CDCl_3$ solution) was found for the former in *N*-methylsalicylaldimine [18], whilst for the latter a strength of about 29 kJ/mol was

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predicted by Schroeder and Lippincott [19] according to their potential function model when $r_{N\cdots O}$ is 2.7 Å. Experimentally, no example of a strong N—H···O hydrogen bond is known [1].

No theoretical study has been found in the literature on simple CAs, apart from STO-3G calculations on EI and 2-hydroxybenzylidenamine with an O—H···N bridge [20] and a report in the PhD thesis of one of us [21], based on semiempirical Austin model 7 and Parameterized model 3 Hamiltonians and, limited to the most interesting conformations, on ab initio calculations at the 6-31G* level. Neglecting the contrasting results of the semiempirical methods, the standard ab initio 6-31G* calculations predicted the CI form to be more stable than the EI one (ΔE = 13.9 kJ/mol), in contrast with experimental findings.

In the present work the results arising from a more careful ab initio investigation, performed using a more extended basis set with inclusion of the correlation energy at second-order Møller-Plesset (MP2) and Becke's three parameter hybrid with the correlation functional of Lee, Yang and Perr (B3LYP) levels are discussed. The main aims are the determination of the order of stability of the various conformations in connection with the theoretical evaluation, in the gas phase and in water solution, of the energies (E_{HB}) of the various hydrogen bridges present in the three tautomers. The knowledge of such energies is of capital importance both for rationalizing the conformational equilibrium and for better understanding the interactions governing the hydrogen-bridge formation in the gas phase as well as in water, which is the main component in biological environments.

2 Calculations

All the theoretically possible conformations of CA and of its tautomers CI and EI were fully optimized, without geometry constrictions, at the ab initio level of calculations using the Gaussian94 [22] and Gaussian98 [23] programs. The standard 6-31G** basis set was adopted, whilst the correlation energy was evaluated both at the MP2 level and following density functional theory by adopting the Becke functional [24–26].

Optimization of the molecular geometries in water solution was carried out according to the polarizable continuum method of Tomasi and coworkers, which exploits the generating polyhedra procedure [27–35, and Refs. therein] to build the cavity in the polarizable continuum medium where the solute is accommodated. The cavity is defined as the envelope of spheres centred on atoms (or group of atoms). Other spheres, not centred on solute atoms, are automatically added during calculations to mimic the "solvent excluding surface", i.e. the surface touched by the solvent (described as a sphere rolling on the solute). In the present calculations the van der Waals radius suggested by Bondi [36] was assigned to each solute atom. Only single-point calculations were performed at the MP2 level since in this case the Gaussian98 program does not allow optimization of the molecular geometry. Calculations were carried out on a Sun Ultra1 workstation and on a Pentium II personal computer.

3 Results and discussion

3.1 Molecular geometry

For the three tautomers, CA, EI and CI, all the possible conformations (4, 16 and 8, respectively) were considered. Their order of stability is reported in Table 1. For space-saving, only the B3LYP/6-31G** optimized geometries (in the gas phase and in water solution) concerning the most important conformations are reported. MP2/6-31G** geometries (only the gas

Table 1. Gas-phase order of stability of the conformations of carbonylamine (*CA*) tautomers (energies in kilojoules per mole)

	ΔE[a] 6-31G*	ΔE[b] MP2/6-31G**	ΔE[b] B3LYP/6-31G**		ΔE[a] 6-31G*	ΔE[b] MP2/6-31G**	ΔE[b] B3LYP/6-31G**
CA-1	0.00	0.00[c]	0.00[c]	EI-1	0.00	0.00[e]	0.00[e]
CA-2	13.39	21.92	22.49 (19.34)	EI-2	47.26	55.65	60.66 (60.89)
CA-3	14.70	20.20	22.06 (18.42)	EI-3	60.39	68.67	71.86 (70.48)
CA-4	27.83	33.13	34.45 (31.42)	EI-4		52.01	59.04
				EI-5		47.07	50.91
CI-1	5.78	6.34 (6.45)	3.29 (3.89)	EI-6		52.21	55.72
CI-2	26.78	20.20	21.15 (18.85)	EI-7		53.69	58.39
CI-3	8.14	10.49 (9.20)	6.10 (5.80)	EI-8		60.79	65.26
CI-4	0.00	0.00[d]	0.00[d]	EI-9		48.33	50.46
CI-5	19.17	–	–	EI-10		47.85	51.22
CI-6	0.79	2.54 (2.75)	2.81 (3.05)	EI-11		51.83	54.95
CI-7	15.75	10.22 (9.98)	7.45 (7.59)	EI-12		48.43	53.24
CI-8	12.60	7.84	6.54 (6.32)	EI-13		42.59	44.91
				EI-14		49.58	51.27
				EI-15		39.05	42.80
				EI-16		48.89	51.76

[a] Ref. [21]
[b] In *parentheses* the values corrected for the zero-point vibrational energy
[c] E = −246.563447 au (MP2); E = −247.296673 au (B3LYP)
[d] E = −246.548674 au (MP2); E = −247.273295 au (B3LYP)
[e] E = −246.552651 au (MP2); E = −247.284756 au (B3LYP)

phase) are available upon request as supplementary tables. The present results predict that the heavy atom skeletons of the four conformations of the CA tautomer (Fig. 1) are fully planar (Table 2). Their order of stability is

$$\text{CA-1} > \text{CA-2} \cong \text{CA-3} > \text{CA-4}$$

and it does not change if the correlation energy is evaluated according to B3LYP or MP2 approaches. When the zero-point vibrational energy is taken into account CA-3 becomes slightly more stable than CA-2. In agreement with X-ray [11] and IR [12–15] findings concerning substituted CA, CA-1 is the preferred conformation owing to its hydrogen bridge, which forces the amino group to sp^2 hybridization and increases the conjugation inside the chelate ring.

The EI tautomer is quite interesting, since it shows two types of intramolecular hydrogen bonding, i.e. O—H···N and O···H—N (EI-1 and EI-2, respectively). These two types of interactions may be expected to arise from the amino ↔ imino tautomerism

$$=\text{N—H}\cdots\text{O—C} \leftrightarrow \text{N}\cdots\text{H—O—C}$$

even if a suitable N···H···O configuration, confirming such interconversion, was not observed in crystal structures [1] and the symmetry requirement for a proton-tunnelling process is lacking in the ground state [37]. The present results predict that, if EI-4, EI-7 and EI-8 are excluded, the conformations of the EI tautomer (Fig. 2) are also fully planar. EI-1 is the most stable of them and its energy is 31.28 (B3LYP/6-31G**) or 28.34 (MP2/6-31G**) kJ/mol higher than that of CA-1. It is followed by EI-15 and EI-13, whose energies, in turn, are about 40–44 kJ/mol above that of EI-1. Analysis of the geometrical parameters evidences that bond angles in the EI-1 chelate ring are closer to the standard sp^2 hybrid-

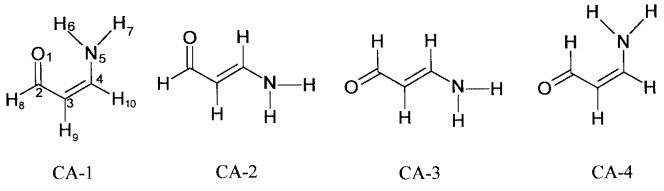


Fig. 1. Possible conformations of carbonylamine (*CA*) and adopted numbering system

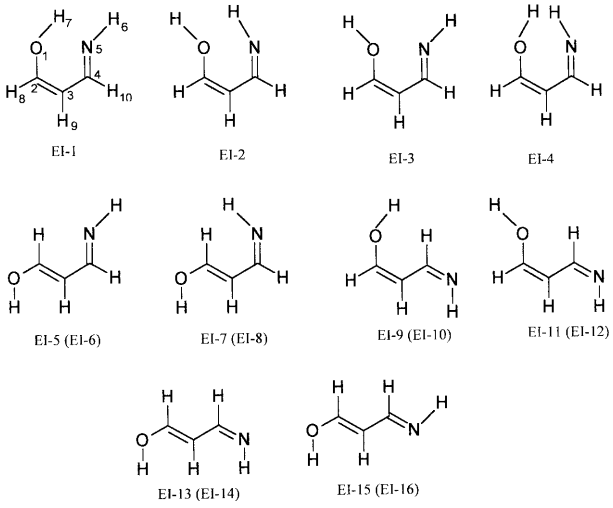


Fig. 2. Possible conformations of enolimine (*EI*) and adopted numbering system. In *EI-6*, *EI-10* and *EI-12* the NH group is rotated by 180° with respect to the position shown in *EI-5*, *EI-9* and *EI-11*. In *EI-8*, *EI-14* and *EI-16* the OH group is rotated by 180° with respect to the position shown in *EI-7*, *EI-13* and *EI-15*

Table 2. Optimized geometries of the most important conformations of (*CA*) and enolimine (*EI*) (B3LYP/6-31G**; distances in angstroms, angles in degrees). Values in *parentheses* refer to water solution

	CA-1	CA-2	CA-3		EI-1	EI-2	EI-3
$r_{1\text{-}2}$	1.241 (1.250)	1.227 (1.241)	1.222 (1.235)	$r_{1\text{-}2}$	1.321 (1.328)	1.362 (1.351)	1.350 (1.346)
$r_{2\text{-}3}$	1.436 (1.423)	1.454 (1.432)	1.449 (1.428)	$r_{2\text{-}3}$	1.366 (1.362)	1.344 (1.351)	1.347 (1.351)
$r_{3\text{-}4}$	1.374 (1.383)	1.359 (1.374)	1.357 (1.371)	$r_{3\text{-}4}$	1.439 (1.442)	1.469 (1.458)	1.460 (1.456)
$r_{4\text{-}5}$	1.343 (1.334)	1.354 (1.336)	1.356 (1.337)	$r_{4\text{-}5}$	1.298 (1.297)	1.281 (1.287)	1.283 (1.287)
$r_{5\text{-}6}$	1.019 (1.015)	1.007 (1.011)	1.007 (1.011)	$r_{5\text{-}6}$	1.018 (1.018)	1.024 (1.023)	1.024 (1.024)
$r_{5\text{-}7}$	1.005 (1.009)	1.005 (1.009)	1.005 (1.009)	$r_{1\text{-}7}$	1.020 (1.028)	0.964 (0.969)	0.965 (0.969)
$r_{2\text{-}8}$	1.094 (1.107)	1.113 (1.109)	1.118 (1.113)	$r_{2\text{-}8}$	1.089 (1.088)	1.088 (1.086)	1.090 (1.087)
$r_{3\text{-}9}$	1.083 (1.082)	1.087 (1.084)	1.087 (1.086)	$r_{3\text{-}9}$	1.082 (1.080)	1.086 (1.083)	1.086 (1.083)
$r_{4\text{-}10}$	1.088 (1.086)	1.088 (1.087)	1.089 (1.087)	$r_{4\text{-}10}$	1.096 (1.094)	1.096 (1.095)	1.101 (1.097)
$r_{\text{O}\cdots\text{N}}$	2.692 (2.746)			$r_{\text{O}\cdots\text{N}}$	2.548 (2.531)	2.981 (2.955)	2.909 (2.959)
$r_{\text{O}\cdots\text{H}}$	1.915 (2.003)			$r_{\text{N}\cdots\text{H}}$	1.625 (1.595)	2.192 (2.155)[a]	
$\vartheta_{1\text{-}2\text{-}3}$	125.2 (125.5)	125.6 (126.6)	125.7 (126.4)	$\vartheta_{1\text{-}2\text{-}3}$	124.3 (123.6)	122.9 (123.2)	124.4 (124.7)
$\vartheta_{2\text{-}3\text{-}4}$	121.4 (122.3)	119.5 (120.5)	119.8 (119.1)	$\vartheta_{2\text{-}3\text{-}4}$	120.1 (120.1)	127.4 (126.9)	128.1 (128.9)
$\vartheta_{3\text{-}4\text{-}5}$	124.2 (125.1)	127.2 (127.1)	127.1 (127.1)	$\vartheta_{3\text{-}4\text{-}5}$	120.8 (120.7)	130.0 (129.4)	124.3 (125.1)
$\vartheta_{4\text{-}5\text{-}6}$	116.2 (117.6)	121.2 (121.6)	120.9 (121.7)	$\vartheta_{4\text{-}5\text{-}6}$	113.4 (113.4)	110.2 (109.8)	109.3 (108.8)
$\vartheta_{4\text{-}5\text{-}7}$	121.6 (121.3)	121.1 (120.9)	121.3 (120.5)	$\vartheta_{7\text{-}1\text{-}2}$	105.9 (105.5)	110.0 (110.2)	109.2 (109.0)
$\vartheta_{3\text{-}2\text{-}8}$	115.8 (115.7)	114.5 (114.3)	114.0 (113.7)	$\vartheta_{3\text{-}2\text{-}8}$	122.0 (122.1)	115.9 (115.1)	119.5 (119.6)
$\vartheta_{2\text{-}3\text{-}9}$	119.4 (119.5)	118.8 (118.7)	118.2 (119.8)	$\vartheta_{2\text{-}3\text{-}9}$	119.8 (120.3)	121.1 (120.9)	115.5 (114.7)
$\vartheta_{3\text{-}4\text{-}10}$	120.1 (119.7)	117.5 (117.8)	118.8 (118.8)	$\vartheta_{3\text{-}4\text{-}10}$	117.4 (117.3)	113.8 (114.2)	113.1 (113.3)
$\omega_{1\text{-}2\text{-}3\text{-}4}$	0.0 (0.0)	0.0 (0.0)	180.0 (180.5)	$\omega_{1\text{-}2\text{-}3\text{-}4}$	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
$\omega_{2\text{-}3\text{-}4\text{-}5}$	0.0 (0.0)	179.8 (179.9)	179.8 (179.5)	$\omega_{2\text{-}3\text{-}4\text{-}5}$	0.0 (-0.2)	−0.1 (1.2)	0.0 (0.0)
$\omega_{3\text{-}4\text{-}5\text{-}6}$	0.0 (0.0)	1.6 (1.1)	1.7 (2.1)	$\omega_{3\text{-}4\text{-}5\text{-}6}$	180.0 (180.0)	0.0 (0.0)	180.0 (180.0)
$\omega_{3\text{-}4\text{-}5\text{-}7}$	180.0 (180.0)	177.2 (178.0)	177.7 (178.5)	$\omega_{7\text{-}1\text{-}2\text{-}3}$	0.0 (0.6)	180.1 (178.9)	180.0 (180.0)

[a] $r_{\text{O}\cdots\text{H}}$

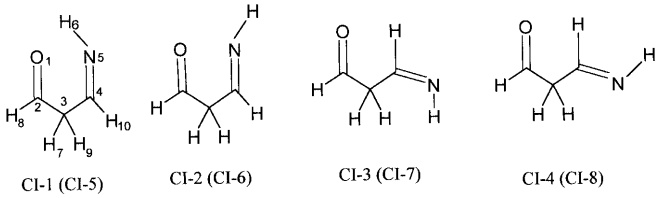


Fig. 3. Possible conformations of carbonylimine (*CI*) and adopted numbering system. In the conformations indicated in *parentheses* the CHO group is rotated by 180° with respect to the position shown in the figure

ization values than in EI-2 (Table 2). The resulting lower strain and the better conjugation deducible from the bond lengths indicate that the O-H···N bridge of the EI-1 conformation is stronger than the N-H···O one present in EI-2. The energies of such bridges are discussed in more detail in the following.

The eight possible conformations of the CI tautomer are shown in Fig. 3. Earlier reports, based on experimental findings concerning CA derivatives [10, 38], suggest that the CI form is less stable than CA and EI. This is mainly due to the breaking of the conjugation between the two double bonds as a consequence of the presence of the CH_2 group. Calculations predict that only the chelate CI-1 conformation is planar, whereas CI-4 is the most stable. No stable local minimum was found for CI-5, since during optimization it always evolves towards CI-1. The minimum energy conformation found for CI-2 is very unstable and easily evolves towards CI-4 (ω_{5432} = 180°). Calculation of the IR spectrum revealed that it is a saddle point, but it is here taken into account as a reference for discussion of the E_{HB} estimate. The greater stability of CI-4 with respect to all the other possible conformations originates mainly from its lower strain, as can be seen by comparing its geometry, in particular r_{34}, ϑ_{234} and ϑ_{345} (Table 3), with that of CI-2. In any case, barring CI-2, the energy differences among the most and the least stable CI conformations are modest, the maximum being about 10 kJ/mol at both B3LYP and MP2 levels.

According to the MP2/6-31G** results, the CI-4 energy is 38.8 kJ/mol above that of CA-1 and increases to 61.4 kJ/mol when the B3LYP results are considered. It is to be noted that the MP2/6-31G** and the B3LYP/6-31G** results are very similar to each other, except for the increase in the energy of CI-4 with respect to CA-1, predicted at the B3LYP level, notwithstanding that the geometries found by the B3LYP approach are negligibly different from those found using the MP2 one. In our opinion the ΔE of 61.4 kJ/mol is overestimated. Such overestimation (which does not change appreciably when the planarity of the heavy atom skeleton is imposed on CI-4) seems to be typical of the B3LYP functional and bound to the breaking of conjugation in the CI isomers. In fact, as can be inferred from the previous discussion, the disagreement appears only when a comparison is made between conjugated and nonconjugated isomers. As a confirmation, it was shown, that also in FMZ the energy difference between the most stable conjugated form (HN=N—CH=N—NH_2, stabilized by an intramolecular N—H···N hydrogen bridge) and the most stable nonconjugated (HN=N—CH_2—N=NH) conformation predicted by MP2/6-31G** calculations (44.1 kJ/mol) is much lower than that predicted by the B3LYP/6-31G** approach (72.1 kJ/mol). However, given the remarkable stability difference between CA-1 and CI-4 also at the MP2 level, the relative population percentages are not affected and both approaches agree in predicting the negligible importance or total absence of the CI isomer in the tautomeric conformational equilibrium. This conclusion agrees with the experimental findings from the IR spectra, which show no absorption band attributable to a free carbonyl group [13, 14].

Table 3. Optimized geometries of the most important conformations of carbonylimine (*CI*). (B3LYP/6-31G**; distances in angstroms, angles in degrees). Values in *parentheses* refer to water solution

	CI-1	CI-2	CI-4
$r_{1\text{-}2}$	1.213 (1.218)	1.206 (1.213)	1.211 (1.216)
$r_{2\text{-}3}$	1.511 (1.504)	1.519 (1.506)	1.515 (1.502)
$r_{3\text{-}4}$	1.518 (1.510)	1.509 (1.506)	1.505 (1.502)
$r_{4\text{-}5}$	1.269 (1.273)	1.270 (1.272)	1.272 (1.272)
$r_{5\text{-}6}$	1.025 (1.025)	1.025 (1.025)	1.025 (1.024)
$r_{2\text{-}8}$	1.113 (1.107)	1.117 (1.110)	1.113 (1.107)
$r_{3\text{-}7}$	1.102 (1.100)	1.103 (1.100)	1.097 (1.100)
$r_{3\text{-}9}$	1.102 (1.100)	1.103 (1.100)	1.102 (1.100)
$r_{4\text{-}10}$	1.098 (1.095)	1.103 (1.098)	1.097 (1.096)
$r_{O\cdots N}$	2.944 (2.916)	2.937 (2.950)	
$r_{O\cdots H}$	2.123 (2.084)		
$\vartheta_{1\text{-}2\text{-}3}$	126.2 (126.0)	127.8 (127.5)	124.6 (124.4)
$\vartheta_{2\text{-}3\text{-}4}$	119.3 (119.3)	121.5 (121.9)	113.9 (113.5)
$\vartheta_{3\text{-}4\text{-}5}$	129.7 (129.1)	124,5 (125.3)	120.4 (121.9)
$\vartheta_{4\text{-}5\text{-}6}$	110.0 (109.6)	109.7 (109.0)	110.2 (109.7)
$\vartheta_{3\text{-}2\text{-}8}$	113.7 (113.8)	111.6 (112.2)	114.5 (114.7)
$\vartheta_{2\text{-}3\text{-}7}$	107.1 (107.2)	106.7 (107.1)	107.8 (106.8)
$\vartheta_{4\text{-}2\text{-}9}$	109.4 (109.5)	108.7 (108.3)	110.6 (110.8)
$\vartheta_{3\text{-}4\text{-}10}$	112.9 (113.2)	112.2 (112.1)	115.2 (115.0)
$\omega_{1\text{-}2\text{-}3\text{-}4}$	0.0 (0.0)	0.0 (0.0)	183.1 (176.0)
$\omega_{2\text{-}3\text{-}4\text{-}5}$	0.0 (−0.4)	0.0 (0.0)	132.5 (124.0)
$\omega_{3\text{-}4\text{-}5\text{-}6}$	0.0 (0.0)	180.0 (180.0)	179.3 (179.3)

3.2 Hydrogen bonding

Detailed data concerning the intramolecular hydrogen bridges of CA-1, EI-1, EI-2 and CI-1 are shown in Table 4. The N—H···O bridges of CA-1 and CI-1 involve the NH_2 and the NH groups, respectively. On the grounds of the related geometrical data and different molecular conjugation, one can infer that the former is certainly stronger than the latter, even if the evaluation of E_{HB} for CA-1 is not simple because a reference conformation obtainable by rotating the NH_2 group is lacking. From the stability differences with respect to the alternative CA-2, CA-3 and CA-4 conformations, the energy of this bridge should be in the range 20–35 kJ/mol. The lowest value – obtained when CA-3 or CA-2 are selected as free-hydrogen-bonding reference conformation – should be the most reliable estimate since such unfolded conformations are less affected by nonbonded interactions than CA-4.

Table 4. Geometrical parameters, net charges and energies of the hydrogen bridges of CA tautomers

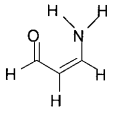
	CA-1		EI-1[a]		EI-2		CI-1	
	B3LYP	MP2	B3LYP	MP2	B3LYP	MP2	B3LYP	MP2
q_{O1}	−0.4992	−0.6344	−0.4913	−0.6430	−0.4913	−0.6232	−0.3839	−0.5059
q_{N5}	−0.5760	−0.7346	−0.6091	−0.7341	−0.5011	−0.5860	−0.4665	−0.5501
q_{H6}	0.3141	0.3806	0.2396	0.2769	0.2415	0.2887	0.2560	0.3055
q_{H7}	–	–	0.3721	0.4489	0.3326	0.3667	–	–
$r_{O\cdots N}$	2.6922	2.6900	2.5482	2.5801	2.9809	2.9401	2.9435	2.9331
r_{N-H}	1.019	1.0130	1.018	1.017	1.024	1.021	1.025	1.021
r_{O-H}	–	–	1.020	1.004	0.964	0.963	–	–
$r_{N\cdots H}$	–	–	1.6254	1.6778	–	–	–	–
$r_{O\cdots H}$	1.9146	1.9273	–	–	2.1923	2.1329	2.1230	2.1050
$\vartheta_{O\cdots H-N}$	130.7	129.7	148.0	147.3	132.5	134.5	136.0	136.7
E_{HB}	22–34.5	20–33	71.86	68.67	11.20	13.02	20.20	21.15
$E_{HB}(1)$[b]	51.54	42.74	74.52	68.29	10.87	9.60	1.26	–

[a] In malondialdehyde: $r_{O\cdots O}$ = 2.5546, $r_{O\cdots H}$ = 1.6410, r_{O-H} = 1.0070, q_{O1} = −0.4994, q_{O5} = −0.4731, q_{H6} = +0.3658 (B3LYP/6-31G**);
$r_{O\cdots O}$ = 2.5930, $r_{O\cdots H}$ = 1.6991, r_{O-H} = 0.9937, q_{O1} = −0.6353, q_{O5} = −0.6215, q_{H6} = +0.4339 (MP2/6-31G**)

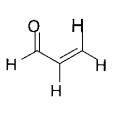
[b] $E_{HB}(1)$ is the hydrogen-bridge energy (kJ/mol) evaluated from rotational barriers (see text)

To lend further support to such a conclusion, attempts to estimate the hydrogen-bond energy from rotation barriers of the donor and acceptor groups were made. Such a method (already applied to MDA and FMZ [9]) assumes that the hydrogen-bond strength can be obtained from the difference between the rotational barrier of the group(s) involved in the bridge and the barrier of the same group in a free-hydrogen-bond reference molecule.

By comparing the rotational barriers of the CHO group in CA-1 (70.52 kJ/mol when calculated at the MP2/6-31G** level and 83.21 kJ/mol if the DFT B3LYP approach is adopted) and in its reference molecule (27.78 and 31.67 kJ/mol, according to the two methods, respectively) (Scheme 2) E_{HB} values of



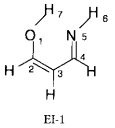
CA-1



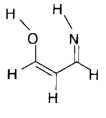
CA-1 Reference molecule

42.74 kJ/mol (MP2) and 51.54 kJ/mol (B3LYP) were obtained. Both of them (in particular that from the B3LYP approach) are higher than the previously discussed estimates even though they are lower than the energy of the O—H···O bridge of MDA. It is very likely that the overestimation is a consequence of the partial reduction of the conjugate system dimension in the reference molecule deriving from substitution of the amino group with a hydrogen atom. In fact, if the CHO rotational barrier calculated in CA-1 is compared with that calculated in CA-2, the resulting hydrogen-bond strengths are 20.6 and 21.6 kJ/mol, according to the MP2 and B3LYP approaches, respectively. These values are in good agreement with that predicted by the potential function model of Schroeder and Lippincott [19], bearing in mind that our results refer to a N—H···O bridge having a bent angle larger than that assumed in Ref. [19]. Attempts to use the rotational barrier of the NH_2 group gave unsatisfactory and contrasting results and are not discussed here. In any case, the best E_{HB} value from this approach is of the same order as that obtained from the CHO rotational barrier. On the other hand, the scaled stretching mode frequency (B3LYP/6-31G**, scale factor = 0.9613) [39] calculated for the N—H moiety involved in the hydrogen bridge of CA-1 is 3321 cm^{-1}, while that calculated for the free N—H is 3580 cm^{-1}, to be compared with the experimental data of 3165 and 3497 cm^{-1} concerning 4-(2′-cianoethyl)amino-3-penten-2-one [10] in tetrachloride solution. The resulting $\Delta\nu$ (259 cm^{-1}) is about a third of that found in MDA and it seems to be in line more with the previously cited E_{HB} values of 20–22 kJ/mol than with the higher ones.

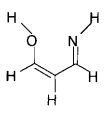
The strengths of the O—H···N (EI-1) and N—H···O (EI-2) bridges, present in the EI tautomer, can be evaluated as stability differences with respect to EI-3 (Scheme 3):



EI-1



EI-2



EI-3

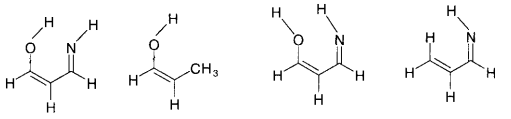
Using this method, the O—H···N is a very strong bridge, its energy (68.67 and 71.86 kJ/mol according to MP2 and B3LYP calculations, respectively) being even stronger than is found for the O—H···O bridge of MDA (58.61 and 62.84 kJ/mol, according to the two approaches, respectively [40]). This result is supported by the N···O and N···H distances (which are shorter than the O···O and O···H ones found in MDA) and by the increased net charges on O, N (more negative than in MDA) and H (more positive than in MDA) atoms, which enhance the electrostatic contribution. A further plausible explanation for this result can be due to the better stabilizing interaction between the N lone pair and H_7 with respect to the O lone pair of MDA. The energies obtained are higher than the 40.6 kJ/mol reported in the literature for the O—H···N bridge of *N*-methylsalicyl-

aldimine [18], but are in line with the value of 66.1 kJ/mol previously calculated for EI-1 at the STO-3G level [20] (from B3LYP/6-31G** test calculations on *N*-methylsalicylaldimine, E_{HB} = 60.5 kJ/mol was obtained by the present authors; it lowers to 48.7 kJ/mol when calculated in chloroform solution).

On the grounds of the very long O···N and O···H distances (which are nearly equal to the sum of the van der Waals radii of the atoms involved) and to the lower net charges predicted on the atoms involved, the N—H···O hydrogen bridge in EI-2 is expected to be even weaker than that of CA-1. The E_{HB} values estimated as stability differences with respect to EI-3 are 13.02 (MP2) and 11.20 kJ/mol (B3LYP).

These estimates are also confirmed when the appropriate rotational barriers are taken into account.

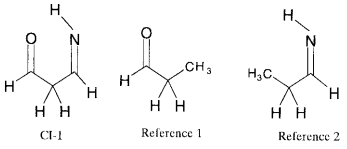
In fact, comparison between the OH barrier calculated for EI-1 (83.71 and 91.49 kJ/mol, according to MP2 and B3LYP results) and for its reference molecule (15.42 and 16.97 kJ/mol, at MP2 and B3LYP level, respectively) gives E_{HB} values of 68.29 and 74.52 kJ/mol for the O—H···N bridge (Scheme 4). As far as the



N—H···O hydrogen bridge is concerned, comparison between the MP2 (22.08 kJ/mol) and B3LYP (26.92 kJ/mol) rotational barriers calculated for the C=N—H group in EI-2 and in its reference molecule (12.48 and 16.05 kJ/mol, according to the two approaches, respectively) produces E_{HB} values of 9.60 (MP2) and 10.87 (B3LYP) kJ/mol. They are in very good agreement with those from a comparison of the C=N—H barriers in EI-1, EI-2 and EI-3 (84.82, 26.93 and 21.79 kJ/mol at the B3LYP level and 73.43, 21.09 and 13.55 kJ/mol at the MP2 level), which give E_{HB} values of 63.03 and 5.14 kJ/mol (B3LYP) or 59.88 and 8.54 kJ/mol (MP2) for the O—H···N and N—H···O bridges, respectively. The high energy of the O—H···N hydrogen bridge is also in line with the resulting $\Delta\nu$ (984 cm^{-1}, B3LYP/6-31G**) between the stretching mode frequencies (scaled values) of the O—H group in EI-3 (3658 cm^{-1}) and EI-1 (2674 cm^{-1}).

In CI-1, the N···O and O···H distances are longer by far than in CA-1 and EI-1 so a very weak hydrogen bond strength is conceivable. When energy estimates are deduced as stability differences with respect to the CI-2, E_{HB} is 20.20 kJ/mol (MP2/6-31G**) or 21.15 kJ/mol (B3LYP/6-31G**). In contrast, if one of the other possible conformations is selected as an alternative reference form, E_{HB} ranges from a minimum of 2.5–2.8 to a maximum of 10.5 kJ/mol. These latter results are more reliable values and are also supported by the shifts of the N—H stretching mode frequencies since the maximum $\Delta\nu$ between the frequency predicted for CI-1 (3323 cm^{-1}, B3LYP/6-31G**, scaled value) and the corresponding ones of the other conformations (free N—H) is lower than 50 cm^{-1}. Then, E_{HB} coming from comparison with CI-2 appears to be suspect because the hydrogen bridge appears to be stronger than the analogous bridge in the EI-2 isomer, where conjugation is present. Indeed, as pointed out in the previous section, the CI-2 conformation is a saddle point on the potential surface so it could not be reliable in a stability comparison.

The reliability of a low E_{HB} value is once again supported by comparing the B3LYP/6-31G** rotational barriers of the CHO (10.73 kJ/mol) and CH=NH (9.58 kJ/mol) groups in CI-1 and in the related reference molecules (9.50 kJ/mol in reference 1 and 8.32 kJ/mol in reference 2, Scheme 5). In both cases the E_{HB} value



obtained is about 1.2 kJ/mol, attributable to weak electrostatic interactions, as in the corresponding tautomer of FMZ; however, whatever the actual E_{HB} value in CI-1 is from comparison with CA and EI the relevant effect of conjugation in strengthening the intramolecular hydrogen bridges is evident.

3.3 Proton transfer

The previously cited amino ↔ imino tautomerism implies the transfer of a proton from the nitrogen to the oxygen atom and vice versa, through an intermediate position of hydrogen in the N···H···O configuration. This situation has not been observed in the crystal structures of CAs [1]. It has been pointed out that the lack of the symmetry requirement (which, in contrast, is present in the strong O···H—O bond) prevents the possibility of proton tunnelling in the ground state of the title compounds [37]. Indeed, proton transfer could occur during vibration if the barrier associated with the tautomerization pathway was not prohibitive. In fact a tautomeric equilibrium mixture of rapidly interconverting enol and enethiol forms was observed in several β-thioxoketones in the gas phase and in solution [41]. In particular, for thiomalondialdehyde, whose enol and enethiol conformations differ very little in energy [42], a proton-transfer barrier of 13.5 kJ/mol (which lowers to about 8.5 kJ/mol after zero-point-energy correction) was calculated at the G2(MP2) level of theory [43]; no details were given in that report on the S···O distance variation along the tautomerization pathway.

To have information on the possibility of the CA-1 ↔ EI-1 tautomerization, the potential-energy curves at different O···N distances versus r_{OH} were calculated at the MP2/6-31G** level (Fig. 4). What one notes is that on decreasing the distance between the heteroatoms involved in the hydrogen bridge the minimum of the less stable tautomer disappears. The hypothetical transition state should be a structure in which the hydrogen atom is equidistant from the two heteroatoms of the bridge. If such a condition is imposed and all the geometrical parameters are optimized, the resulting $r_{N\cdots O}$ distance is

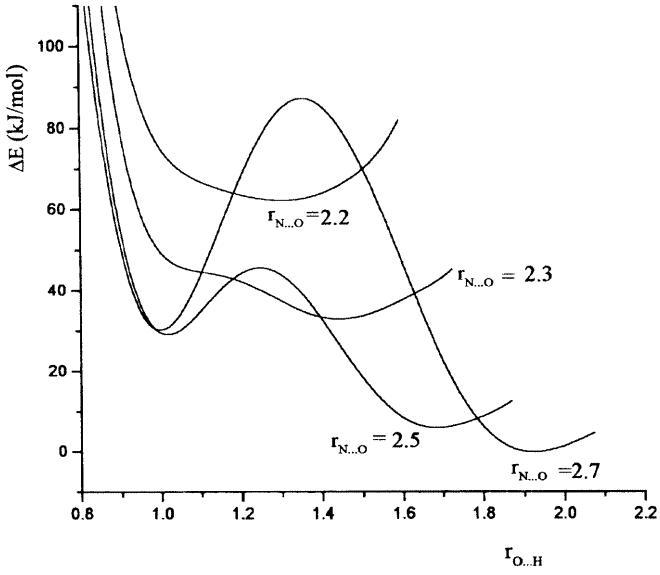


Fig. 4. Potential-energy curves calculated for fixed O···N distances in CA

2.388 Å. At this distance the resulting interconversion barrier is 37.3 kJ/mol, which evidences that the proton-transfer process in CA is more difficult than in the previously cited sulphurated compound, where it could be described as an intramolecular vibrational relaxation process. It is worthy mentioning the good agreement between the $r_{N\cdots O}$ value calculated here for the pseudo-hydrogen-centred N···H···O bridge and that (about 2.50) estimated when considering the differences in the bond and van der Waals radii with respect to the O···H···O case [44].

3.4 Water solution

It is known that the hydrogen-bond strength in solution is weaker than in the gas phase and its energy decreases on increasing the dipole moment of the solvent. As a consequence, the conformational equilibrium could also undergo remarkable changes. To study the geometry and the hydrogen-bond-energy changes, B3LYP/6-31G** optimization in water solution was also carried out, whilst only single-point calculations were performed at the MP2/6-31G** level.

Analysis of the results obtained (Table 5) indicates that the order of stability among the most stable CA-1, EI-1 and CI-1 tautomers does not change. Some stability inversions occur in the EI series (e.g. EI-13 becomes more stable than EI-15 after solvation), but they are of negligible importance because isomers far less stable than EI-1 are involved. After geometry optimization in water, ΔE of CI-1, CI-3 and CI-6 with respect to CI-4 becomes lower than 2 kJ/mol.

A comparison of the total energies in the gas phase and in solution (Table 5) is also interesting because it points out that full optimization in a solvent (much too time consuming because self-consistency in many cases is difficult to achieve) is often not necessary since only

Table 5. Order of stability and energetic data of CA tautomers in water solution (energies in kilojoules per mole)

	MP2/6-31G**		B3LYP/6-31G**		
	Order of stability[a]	$\Delta E_{gas-sol}$[b]	Order of stability[a]	$\Delta E_{gas-sol}$[b]	$\Delta E_{gas-sol}$[c]
CA-1[d]	0.00	19.49	0.00	23.94	25.35
CA-2	11.48	29.92	7.93	37.68	39.91
CA-3	6.65	33.04	2.27	42.86	45.14
CA-4	21.61	31.00	16.57	38.39	43.24
EI-1[e]	0.00	10.71	0.00	11.57	11.86
EI-2	32.29	34.08	38.35	33.73	34.17
EI-3	44.14	35.24	46.42	36.97	37.30
EI-5	33.47	24.31	36.90	25.51	25.86
EI-9	32.81	26.24	35.33	26.54	26.99
EI-10	32.41	26.16	31.08	26.72	27.00
EI-13	23.44	29.86	25.64	30.68	31.13
EI-15	22.50	37.11	26.29	27.85	28.37
CI-1	4.52	19.02	1.97	20.44	20.94
CI-2[f]	18.99	24.45	14.41	24.69	29.66
CI-3	6.30	20.99	1.75	23.17	23.98
CI-4[g]	0.00	16.79	0.00	18.69	19.63
CI-6	2.03	17.29	1.81	19.80	20.62
CI-7	8.48	18.53	5.83	20.56	21.25
CI-8	5.47	19.16	4.38	21.40	21.79

[a] ΔE with respect to the most stable conformation of each tautomer
[b] Energy gain on passing from the gas phase to solution (gas-phase geometry)
[c] Energy gain on passing from the gas phase to solution after full geometry optimization
[d] $E = -246.570869$ au (MP2); $E = -247.306328$ au (B3LYP)
[e] $E = -246.556733$ au (MP2); $E = -247.289273$ au (B3LYP)
[f] For the reliability of this conformation see text
[g] $E = -246.555070$ au (MP2); $E = -247.280771$ au (B3LYP)

modest changes are noted with respect to the geometrical parameters obtained in the gas phase (on the whole, bond angle variations are less than 2° and bond length changes are limited to about 0.01 Å at the most, Tables 2, 3).

The main energy gain is obtained on passing from the gas phase to solution and maintaining the gas-phase geometry (first iteration); further energy gain due to geometry optimization in the solvent is almost negligible in most cases. In the molecules considered here the maximum of the latter gain is about 4.9 kJ/mol and was found in the CA-3 and CI-2 isomers. Since cavitation and dispersion energy terms nearly balance each other, being of the same order and having opposite signs, the main contribution to the stabilization of the molecules in solution comes from the "solute–solvent" polarization energy.

The hydrogen-bond energy, evaluated as the stability difference with respect to a non-hydrogen-bonded conformation, undergoes a very strong decrease with respect to the gas phase. In fact, E_{HB} concerning the N—H···O bridge lowers to the range 6–15 kJ/mol for CA-1 (gas phase: 22–35 kJ/mol), 8.07 kJ/mol for EI-2 (gas phase: 11.20 kJ/mol) and 12.44 for CI-1 (gas phase: 21.15 kJ/mol). E_{HB} for the O—H···N bridge (EI-1) lowers to 38.35 kJ/mol (gas phase: 60.66 kJ/mol). Analogous results are observed when the MP2/6-31G** results are analysed. However, the E_{HB} lowering and the solvation

Table 6. Geometries (B3LYP/6-31G**) and energies of CA ions (distances in angstroms, angles in degrees, energies in kilojoules per mole)

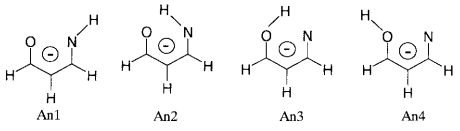
	An1[a]	An2[b]		An1	An2
$r_{1\text{-}2}$	1.258 (1.266)	1.245 (1.259)	$\vartheta_{1\text{-}2\text{-}3}$	129.1 (128.2)	131.5 (130.1)
$r_{2\text{-}3}$	1.403 (1.399)	1.414 (1.403)	$\vartheta_{2\text{-}3\text{-}4}$	124.7 (124.1)	130.0 (128.2)
$r_{3\text{-}4}$	1.434 (1.430)	1.424 (1.427)	$\vartheta_{3\text{-}4\text{-}5}$	130.8 (129.5)	122.4 (128.0)
$r_{4\text{-}5}$	1.302 (1.305)	1.310 (1.308)	$\vartheta_{4\text{-}5\text{-}6}$	105.7 (105.8)	107.3 (107.6)
$r_{5\text{-}6}$	1.028 (1.027)	1.027 (1.023)	$\vartheta_{3\text{-}2\text{-}8}$	113.2 (114.1)	110.7 (112.2)
$r_{2\text{-}8}$	1.129 (1.117)	1.135 (1.121)	$\vartheta_{2\text{-}3\text{-}9}$	117.5 (117.1)	114.7 (115.9)
$r_{3\text{-}9}$	1.091 (1.084)	1.092 (1.086)	$\vartheta_{3\text{-}4\text{-}10}$	114.1 (114.9)	111.0 (112.4)
$r_{4\text{-}10}$	1.108 (1.101)	1.113 (1.103)	$\vartheta_{O\cdots H\text{-}N}$	137.0 (138.6)	–
$r_{O\cdots N}$	3.060 (2.983)	3.251 (3.131)			
$r_{O\cdots H}$	2.227 (2.134)	–			
ΔE (gas)	43.2	0.0			
ΔE (water)	20.5	0.0			
ΔE (gas-water)	268.2	245.5			
E_{dep} (gas)	1602.5	1559.3			
E_{dep} (gas)	1359.7	1339.2			

[a] E(gas) = −246.686297 au; E(water) = −246.788460 au
[b] E(gas) = −246.702748 au; E(water) = −246.796250 au

stabilization do not indicate an equilibrium shift towards the EI-1 tautomer since its ΔE with respect to CA-1 is about 13 kJ/mol higher than in the gas phase according to the B3LYP results. It is very likely that specific interactions between solvent and the hydrogen-bridged atoms, in addition to the effect of the polarity of the solvent cavity, could improve these results.

3.5 Deprotonation energy

The most stable CA tautomer, CA-1, has two amino protons and the molecule can be deprotonated by removing any of them, with possible formation of the An1 and An2 anions (Scheme 6), depending if the free



proton or the proton involved in the intramolecular hydrogen bond is removed. The same anions plus An3 and An4 can be obtained if EI-1, EI-2 or EI-3 conformations are deprotonated. An3 shows no local minimum since during optimization the proton bonded to oxygen migrates towards the nitrogen atom and An2 is once again obtained; An4 is less stable by far than An1 (ΔE = 289 kJ/mol) and will not be taken into account.

A comparison between the geometrical parameters of the anions (Table 5) and those of the neutral CA-1 conformation points out a lengthening of the double bonds and a shortening of the single bonds of the chelate ring, which indicate an increased conjugation in the anions. At the same time, the increased O···N repulsion deriving from the greater negative net charges on the two heteroatoms produces a widening of the bond angles with respect to those of CA-1, with a consequent lengthening of the O···N and O···H distances.

The deprotonation energy, E_{dep}, evaluated as the difference between the energy of the anion and that of the neutral molecule, is 1559.3 kJ/mol for the An2 anion and 1602.5 kJ/mol (1523.1 and 1563.6 kJ/mol after zero-point-energy corrections) for the An1 anion, at the B3LYP level (the MP2 values are 1560.0 and 1608.9 kJ/mol, respectively). E_{dep} for An1 is higher than that of An2 because in the latter the proton removed is that involved in the hydrogen bond; therefore, it is less acidic than the free proton of An1. Comparison with E_{dep} calculated for MDA (1522.4 and 1528.6 kJ/mol at the B3LYP and MP2 levels, respectively) reveals that CA is less acidic than MDA itself, in agreement with the sligthly stronger hydrogen bridge and with the stronger N—H bond with respect to the O—H one. The strengths of the An2 N—H···O bridge is 48.9 and 43.2 kJ/mol according to the MP2 and B3LYP approaches, respectively; they reduce by about 50% in water solution. These values found for the ion support our opinion that the most reliable strength in the neutral CA-1 conformation should be lower and not far from a mean value deducible from the various estimates discussed in previous sections.

5 Conclusions

On the grounds of the results obtained in the present study and in agreement with experimental findings concerning CA derivatives, CA-1 is the main conformation present in the CA tautomeric equilibrium both in the gas phase and in water solution, whilst the carbonyl imine tautomer should be absent. Proton tunnelling between CA-1 and EI-1 is forbidden owing to a lack of symmetry, whilst the relevant barrier to be overcome does not allow the possibility of proton transfer. The most probable value of the strength of the N—H···O hydrogen bond should be in the range 20–30 kJ/mol in CA-1; it decreases to about 10 kJ/mol in EI-2 and practically vanishes in CI-1. The strongest bridge is the O—H···N one present in EI-1. Its strength is slightly greater than that of the O—H···O bridge of MDA, as also confirmed by the deprotonation energy values. All the bridges discussed are strongly weakened in water solution, even if the conformational equilibrium is not

affected. As expected intuitively, the deprotonation energies showed that the free hydrogen atom is more acidic than that involved in the hydrogen bridge, which, in turn, is less acidic than that of the O—H group of MDA. Calculations also predict that in water solution CA-1 and MDA have comparable acidity.

For EI-1, EI-2 and CI-1 conformers, the E_{HB} energies evaluated from the appropriate rotational barriers are in very good agreement with those estimated as stability differences with respect to the reference structures obtained after 180° outside rotation of the hydrogen-bridged atom.

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