Quantumchemical Interpretation of Regioselectivity in Michael-additions and Protonations

Theses of doctoral (PhD) dissertation

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Introduction

The Michael additions of α,β-unsaturated dicarboxylic acids and their derivatives are commonly used in the syntheses of amino-dicarboxylic acids. Several methods have been developed in the Department of Pharmaceutical Chemistry, Semmelweis University, starting from maleic and fumaric acid derivatives (ester, amide, anhydride), developing thus selective syntheses of the amide and ester derivatives of N-methyl-aspartate and N-methyl-isoaspartate. In these reactions, however, regioselectivity and its interpretation remained a crucial question for a long time.

Famotidine is one of the most widely used gastric acid inhibitors, despite its old-fashioned nature. It is a major question, if its guanyl-thiazole moiety protonates on the thiazole ring or on the guanyl site. Starting from propositions based on experimental and semiempirical theoretical results found in the literature, ab initio calculations were performed on the protonation isomers of the N-(4-mercaptomethyl-thiazolyl)-guanidine according to energetical relations and the presence of intramolecular hydrogen bonds.

Objectives

Regioselectivity of the Michael addition of ammonia on methyl-maleamate

The addition of ammonia and substituted primary amines to methyl maleamate (**m**) may lead to two reaction products (Fig. 1.), forming amino group on the vinylogue carbon of the ester group results in production of isoasparaginates (**i**), the attack on the vinylogue carbon of the amide group leads to asparaginate (**a**) derivatives. The formation of methyl asparaginate was only found in the case of ammonia, the reaction with any other amine led exclusively to methyl isoasparaginate (by ^{1}H NMR spectrum of product mixture).

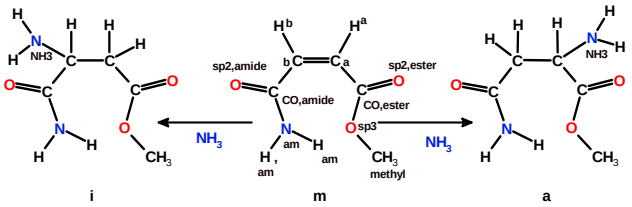


Fig. 1. Michael addition of ammonia on methyl-maleamate

The purpose was to reveal the reasons of regioselectivity stemming from structural, electronic and thermodynamical reasons. It was necessary to do calculations on the starting α,β-unsaturated dicarboxylic acid mixed ester/amide, on the reaction products, and on the possible transition states as well. As simplest model, the additions of the ammonia were investigated.

Geometry and charge distribution of the gross neutral protonation forms of N-(4-mercaptomethyl-thiazolyl)-guanidine

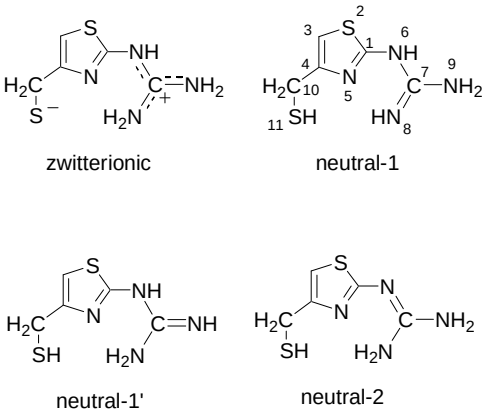


Fig. 2. The investigated protonation forms of N-(4-mercaptomethyl-thiazolyl)-guanidine

The relative energies and charge distributions of four protonation isomers of N-(4-mercaptomethyl-thiazolyl)-guanidine - as models of the correspondig structural unit in famotidine - were investigated: one zwitterionic and three non-charged ones (Fig. 2.).

Methods, instruments

The calculations were performed by a SGI Octane workstation, and for transition states, also by the supercomputer of the Ohio Supercomputer Center.

Regioselectivity of the Michael addition of ammonia on methyl-maleamate

The first steps were the initial *MMFF94s* geometry optimizations (*SYBYL 7.0* software), in order to reduce the number of geometry optimization steps in the quantumchemical calculations. The quantumchemical calculations were performed by the *Gaussian03* software. For methyl-maleamate, the conformational PES for the $C_{CO,amide}$-C_b and $C_{CO,ester}$-C_a rotating bonds was scanned in 60° steps within the [-180°, +180°] range, at the B3LYP/6-31+G(d) level, in vacuo. The quasi-minima were then fully optimized in vacuo to the **m1** and **m2** (Fig 3.), at the B3LYP/6-31+G(d) level and in methanol at the IEF-PCM/B3LYP/6-31+G(d) level. The **m3** and the **m4** conformers (Fig 4.), as well the product structures were fully optimized (the latter ones only in solvent) directly from the MMFF94s geometries. At the levels above, the thermodynamic quantities and the vibrational spectra were also calculated. The exact E_{int} and E_{tot} in vacuo, and in methanol were computed at the B3LYP/6-311++G(2df,2pd) level. Molecular orbitals and partial charges (*NPA*, *CHelpG* and *MKS*) were calculated both with the 6-31+G(d) and 6-311++G(2df,2pd) bases. For transition states optimizations and thermodynamics we have started from the van der Waals complexes of ammonia and **m1**, verifying the results of TS search by visualization of the vibrations corresponding to imaginary

frequencies. E_{int} and E_{tot} were calculated at the IEF-PCM/B3LYP/6-311++G(2df,2pd) and the IEF-PCM/MP2(FC)/6-311++G(2df,2pd) levels.

Geometry and charge distribution of the gross neutral protonation forms of N-(4-mercaptomethyl-thiazolyl)-guanidine

Geometries were optimized at the B3LYP/6-31++G(2d,p) level, in vacuo, and they were verified by the vibrational spectra. Energies were calculated at the B3LYP/6-31++G(2d,p), HF/6-311++G(2df,2pd) and MP2/6-311++G(2df,2pd) levels. The in vacuo free energies ΔG_{tot} were calculated as the sum of ΔE_{el} electron-energies and the thermal corrections (T=298K) ΔG_{298} (kcal/mol). Relative values were compared with the ones of the lowest energy protonation form. Charges were calculated at the B3LYP/6-31++G(2d,p) and MP2/6-311++G(2df,2pd) levels, via Mulliken, NPA, MKS and CHelpG methods.

Results

Regioselectivity of the Michael addition of ammonia on methyl-maleamate

The title molecule bears rigorous structural constraints. Due to π-electron delocalization over the whole molecular backbone, high stability against rotations around the skeletal carbon-carbon single bonds (Figs. 3 and 4) is expected. In the studied C-C=C-C *cis* isomer, considerable repulsion is also expected between the oxygens of the end-groups in some arrangements. Such repulsion does not exist in the C-C=C-C *trans* isomer.

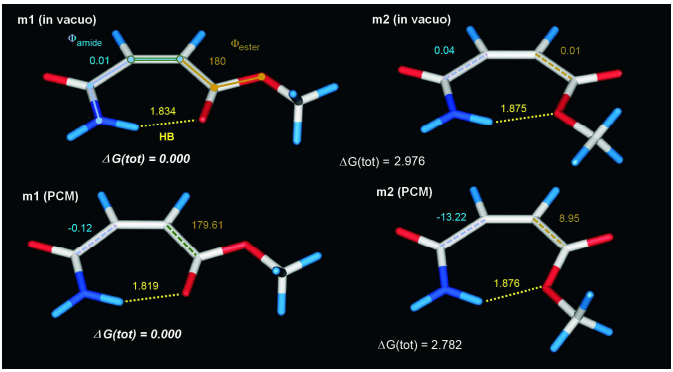


Fig. 3. Planar conformers of methyl maleamate, with the correspondig energies (investigated dihedral angles with degree values, hidrogen bond distances in Angstroms, energies in kcal/mol)

Repulsive interactions occur between two carbonyl oxygens, or between the amide carbonyl oxygen and the sp^3 oxygen in the ester group. On the other hand, attractive interactions may arise due to an intramolecular hydrogen bond between an amide hydrogen and any oxygen in the ester group. Furthermore, attractive n-π* interactions

may come into existence in some non-planar forms, when a carbonyl oxygen lone electron pair is nearly perpendicular to the plane of the other carboxylic function, and the two moieties involved can reach the desired proximity.

Two, primarily planar minima were found both in vacuo and in methanol (Fig 3., Table 1.). The deepest minimum was found for **m1** with $\varphi_{amide} \approx 0^{o}$ and $\varphi_{ester} \approx 180^{\circ}$. For **m2** in methanol, the torsion angles deviate by about 10^{o}.

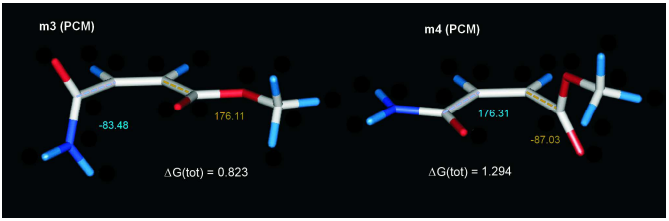


Fig. 4. The conformers of methyl maleamate stabilized by n-π* interactions, with the correspondig energies

Table 1. Relative energies of methyl maleamate conformers in methanol (kcal/mol)

	IEF-PCM/B3LYP/6-311++G(2df,2pd)// IEF-PCM/B3LYP/6-31+G(d)					
	ΔE_{int}	ΔE_{tot}	ΔG_{drc}	ΔG_{solv}	ΔG_{298}	ΔG_{tot}
m1	***0.000***	***0.000***	***0.000***	***0.000***	***0.000***	***0.000***
m2	**5.716**	**3.394**	**0.300**	**3.694**	**-0.912**	**2.782**
m3	**5.682**	**1.293**	**0.980**	**2.273**	**-1.450**	**0.823**
m4	**6.892**	**1.693**	**0.860**	**2.553**	**-1.259**	**1.294**

The two conformers with the carbonyl oxygen donors (referred as **m3** and **m4**), were found in methanol (Fig. 4., Table 1.), but only **m4** was found in vacuo. It is supposed that the proximity of the amide hydrogen and the sp^2 ester oxygen leads to the destabilization of **m3**

and to the conversion of **m1**. The HOMO-2 for **m3** and the HOMO for **m4** nearly correspond to lone pairs of an sp^2 oxygen. By drawing the electron density surface for these orbitals, the orientations of the lobes allow the oxygens acting as donor atoms for n-π* interactions. The symmetry axes of the corresponding lone pairs on the oxygens lie in the line connecting the oxygen and the carbonyl carbon in the other group. Charge distribution calculations of the isolated methyl maleamate can predict the site of the nucleophilic attack, The less negative charge is favorable in this respect. In terms of negativity, the relation $C_a > C_b$ holds with all three methods for conformers **m1**, **m2** and **m3**. Only the natural population analysis (NPA) method predicts slightly more negative charge for C_b in **m4**, but this conformer is a minor component in the equilibrium mixture.

Product conformers and relative energies

The theory could predict energetically the preference of the experimentally observed isoasparaginate product.

Table 2. Relative energies of dominant conformers of ammonia adducts of methyl maleamate in methanol (kcal/mol)

	ΔE_{int}	ΔE_{tot}	ΔG_{drc}	ΔG_{solv}	ΔG_{298}	ΔG_{tot}
i1	***0.000***	***0.000***	***0.000***	***0.000***	***0.000***	***0.000***
i2	**0.082**	**0.694**	**-0.160**	**0.534**	**-0.138**	**0.396**
a1	**4.041**	**0.863**	**0.440**	**1.303**	**-0.658**	**0.645**
a2	**3.453**	**1.516**	**0.230**	**1.746**	**-0.905**	**0.841**

The overall ratio for the isoasparaginate and asparaginate products coming from Boltzmann equation is about 67:33, provided the system is in thermodynamic equilibrium (Table 2.).

Transition state geometries and energies

Two transition states were found, with the ammonia attack on C_a and C_b losing one of its hydrogen that approaches the another carbon (C_b or C_a) results in a C···N···H···C, four-membered quasi-cycle.

Table 3. The relative energies of the transition states(kcal/mol)

	ΔE_{tot} (B3LYP)	ΔE_{tot} (MP2)	ΔG_{drc}	ΔG_{solv} (B3LYP)	ΔG_{solv} (MP2)	ΔG_{298}	ΔG_{tot} (B3LYP)	ΔG_{tot} (MP2)
a	4.081	4.031	1.180	5.261	5.211	-1.212	4.049	3.999
i	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

The vibration with imaginary frequency means the abovementioned "lifting" of the hydrogen. The structures suggest, that the direct 2,3-vicinal bimolecular addition (without methanol involvement) might be a real scene. The other investigations with methanol-mediated models were unsuccessful. Due to the same reactants in both pathways, the preference can be deduced as a direct consequence from the TS energies. By that about 99% is the probability of the isoasparagine product formation (Table 3.).

Geometry and charge distribution of the gross neutral protonation forms of N-(4-mercaptomethyl-thiazolyl)-guanidine

Relative energies

Table 4. The relative B3LYP, HF and MP2 energies and dipole moments of protonation forms (kcal/mol and Debye)

B3LYP/6-31++G(2d,p)

	ΔE_{el}	ΔG_{298}	ΔG_{tot}	dipole moment
zwitterionic	42.71	0.29	43.00	10.5806
uncharged-1	12.55	-0.14	12.41	4.1184
uncharged -1'	8.93	-0.47	8.46	2.8571
uncharged -2	0	0	0	2.9101

HF/6-311++G(2df,2pd) and MP2/6-311++G(2df,2pd)

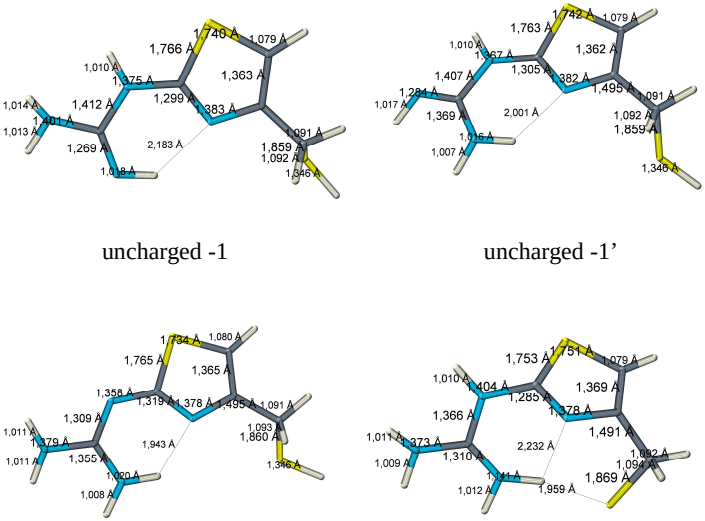
	ΔG_{tot} HF	ΔG_{tot} MP2	dipole moment (Density= MP2)
zwitterionic	51.65	40.98	10.8007
uncharged -1	11.33	11.59	4.0524
uncharged -1'	7.72	8.10	2.8033
uncharged -2	0	0	2.6229

For uncharged structures, the optimization criteria were satisfied, but in the case of zwitterionic one, relatively large displacement were observed, at very small forces. Despite we got all positive frequencies – therefore the optimization step with smallest force was accepted as energy minimum – the further steps of its optimization run, indicated the conversion to the uncharged form, via an

intramolecular proton transfer, that well supported by the large free energy differences, as shown in Table 4. and, in addition to the ones above we got a 1795 cm^{-1} non-imaginary vibration corresponding the proton transfer.

Geometries

As it is observable in the Fig 5., in the uncharged forms the mercaptomethyl moiety is nearly perpendicular to the ring, the dihedral angles between the plane of the thiazole ring, and the C-S bond are 79.4^o and 70.2^o respectively (N_5-C_4-C_{10}-S_{11} angle), while in the zwitterionic particle, due the coulombic attraction of the cationic guanidinium part to the thiolate anion, this angle is 58^o. Further difference is that in the uncharged forms, the guanidine part is almost co-planar with the thiazole ring – 4.7^o and 0.9^o respectively – in contrast to zwitterionic one, in which this co-planarity is broken – dihedral angle (N_5-C_1-N_6-C_7 angle) is 43.8^o by the electrostatic orientation effect of thiolate anion. The different conformation of the mercaptomethyl moiety, but mostly the loss of co-planarity is supposed to be very unfavorable energetically, that may be one of the major driving force in the proton transfer.



uncharged -1 uncharged -1’

uncharged -2 zwitterionic

Fig 5. The geometries of the protonation forms of N-(4-mercaptomethyl-thiazolyl)-guanidine annotated with the bond lengths (also with hydrogen bonds)

Consequences

Regioselectivity of the Michael addition of ammonia on methyl-maleamate

For methyl maleamate, after the conformational PES scan for the C_3-C_4, and C_1-C_2 rotating bonds, two minima with planar geometries were found in vacuo as well in methanol, both stabilized by an intramolecular hydrogen bond between an amide hydrogen and any oxygen in the ester group. By other considerations we obtained in methanol two (in vacuo only one) non-planar structures, stabilized by n-π^* interactions. They were verified by MO coefficients and via graphical representations of the orbitals. Charge distribution calculations of the isolated methyl maleamate can predict the site of the nucleophilic attack: the less negative charge is favored in this respect, and it is proven that the polarisation of the C=C double bond makes preferable the isoasparagine formation. By the relative energies of the products and the transition states, both in case of kinetic, and thermodynamic control we expected to get isoasparagine product. The Boltzmann distribution of the products predicts 2 : 1 proportionally in case of thermodynamic equilibrium. By the energies of transition states, both with DFT and with MP2 methods, in case of kinetic control we should get > 99% isoasparagine adduct. The results are in accordance with the experiments. We have not found transition states for mechanisms involving solvent methanol molecules explicitly.

Geometry and charge distribution of the gross neutral protonation forms of N-(4-mercaptomethyl-thiazolyl)-guanidine

The ab initio/DFT calculations of geometries, energies and charges of protonation isomers of N-(4-mercaptomethyl-thiazolyl)-guanidine show that the most stable form is the one in which the guanidine moiety occurs in the form $N=C(NH_2)_2$ (contains double bond in-between the nitrogen attached to the thiazole ring, and the central guanidine carbon). In addition to this, every isomer contains intramolecular hydrogen bond, it is obviously dominant in the uncharged forms. In the zwitterionic isomer the bond is somewhat looser - due to the deformation of the torsions and bond angles stemming from the electrostatic interaction between the cationic guanidinium part and the anionic thiolate chain - but also exists there. This is otherwise unlikely existing form because of its very high relative energy, and cannot occur in famotidine, where the thiol is etherified. The presence of the hydrogen bond makes it clear, that protonation on the thiazole nitrogen is unfavored. The charge distributions obtained with the different approaches show some ambiguities for the thiazole ring, but not for the N_5 involved in hydrogen bonds, and the charges in the guanidine part have similar tendencies with the different methods and levels of computation.

List of publications

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