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Molecular Determinants for Recognition of Triazole and Tetrazole Analogs of Histamine at H_2-Receptors

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SUMMARY

Calculations of molecular structures, relative stabilities of the various tautomers, and molecular electrostatic potentials (MEPs) were used to examine the molecular properties that determine the actions at H_2-receptors of histamine analogs in which the imidazole ring was replaced by triazole or tetrazole. The analysis indicates that the most stable tautomer of 3-ethylamine-1,2,4-triazole (EATRI), is also the most similar to the assumed active form of histamine. Differences in the MEP of EATRI and histamine are observed mainly near the N(2) nitrogen of EATRI which is the steric equivalent of the C(4) position of histamine. Because EATRI is recognized at the receptor in spite of these differences, we conclude that the H_2-receptor has no selectivity with respect to the electrostatic or steric properties near this position, in agreement with previous observations from structure-activity relations. This conclusion contrasts with the apparent selectivity of the receptor for the reactivity properties of the position equivalent to C(2) in histamine. Thus, the analysis of the tautomeric forms and MEP of the 5-ethylamine-1,2,3,4-tetrazole, which is not recognized by the H_2-histamine receptor, suggests that the negative potential near the N(3) nitrogen, which corresponds to C(2) in histamine, is responsible for the inactivity of this molecule. The mechanism of receptor activation by EATRI is analyzed in relation to results from a theoretical simulation of a proposed activation mechanism of H_2-histamine receptors. We find that the discriminant property for receptor activation by EATRI should be the relative energy of the ring protonated tautomers, and our results indicate that only the cation in which the ring protonation is on N(1) and N(4) and the side chain is anchored at the negative receptor site can be recognized at the histamine H_2-receptor, and can participate in the proposed activation process.

Experimental studies on heterocyclic ethylamines as potential histamine agonists have shown that replacing the imidazole ring by other heterocycles considerably alters their histaminic activity, especially at H_2-receptors (1–3). Some of these compounds were shown to exhibit selectivity on different tissue systems and have since become useful for studying histamine pharmacology (1, 2). Of special importance for understanding the relationship between the structure and the activity of such analogs are compounds in which a small change in structure results in a major change in activity. For example, EATRI (Fig. 1, **1–3**) was found to be a full agonist of histamine with significantly lower potency (1, 3), whereas EATET (Fig. 1, **4** and **5**) was found to be inactive both on H_1- and on H_2-histamine receptors (2). Such compounds, in which one or two carbon atoms in the imidazole ring were replaced by nitrogens, are especially interesting for the study of molecular determinants for recognition and activation at histamine receptors, because differences in the potency or intrinsic activity which result from receptor recognition and activation are ascribable to changes in the properties of the heterocyclic ring. That ring is assumed to be involved in hydrogen bonding at the H_2-receptor site (1, 4, 5).

The triazole ring of EATRI can exist in three different tautomeric forms (Fig. 1). Only one of these forms is equivalent to the N(3)-H tautomer of histamine which is the currently accepted template for recognition at the histamine H_2-receptor (1, 4–8). This alone could explain the observed lower potency of EATRI on the histamine H_2-receptor (1, 3) because the measured potency would be reduced by the fact that, due to the tautomeric equilibrium, only a fraction of the molecules of EATRI would be in the form necessary for recognition of the receptor when equal concentrations of EATRI and histamine are compared. For EATET, the heterocyclic ring can exist in only two different tautomeric forms. The lack of activity of this tetrazole derivative of histamine may be due to its preference for a tautomeric form that is not recognizable at the receptor, in which case it would be neither an agonist nor an antagonist. Alternatively, it is possible that, even if it existed in the required tautomeric form, other electronic properties of the five-mem-

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ABBREVIATIONS: EATRI, 3-ethylamine-1,2,4-triazole; EATET, 5-ethylamine-1,2,4-tetrazole; MEP, molecular electrostatic potential; CHF, coreless Hartree-Fock (method).

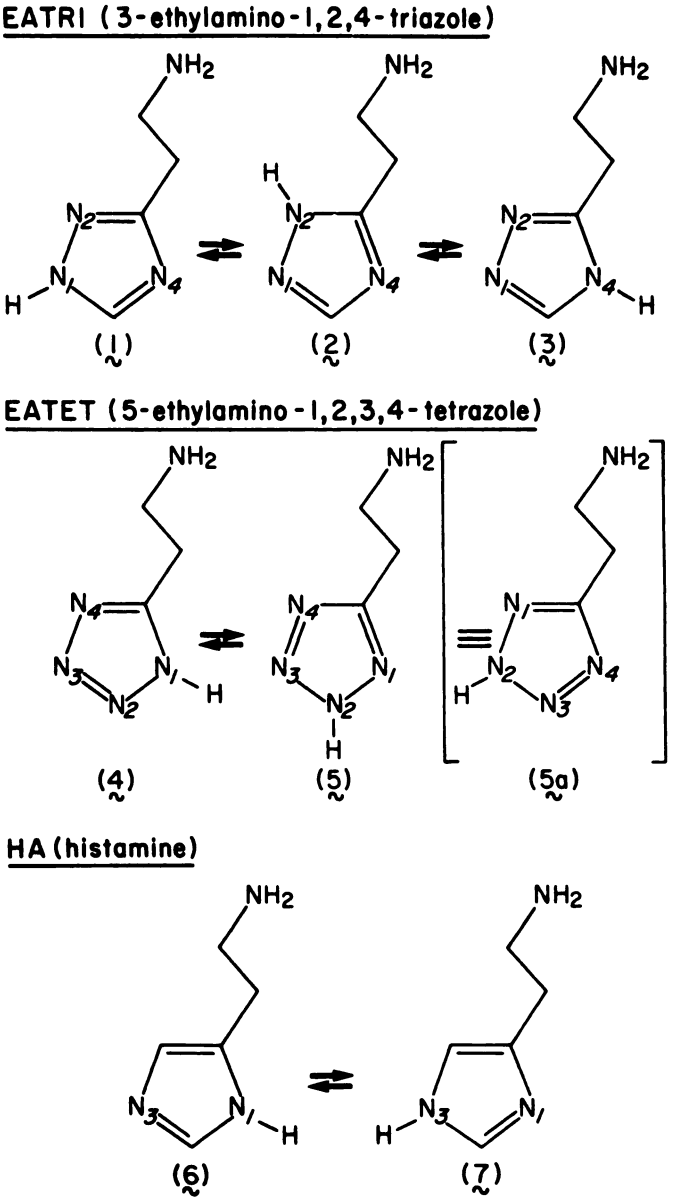

Fig. 1. Molecular structures and numbering schemes for EATRI, EATET, and histamine (HA).

bered ring could prevent its recognition by the histamine H_2-receptor.

These hypotheses linking structures and properties of the molecules to their pharmacological activity can be explored to identify specific molecular determinants that are essential for recognition of both agonists and antagonists at the histamine H_2-receptor. Because EATRI possesses agonistic activity it should be possible to identify also, in addition to the molecular determinants for recognition, the properties of the triazole ring that are responsible for the ability of EATRI to activate this receptor. The analysis of molecular determinants for the activity of congeneric molecules, such as those presented here, on specific receptors is aided by a conceptual separation of the receptor recognition and activation steps (9, 10). This approach is useful here because the effects of a consecutive introduction of nitrogens into the imidazole ring of histamine are interpretable directly as effects on the recognition of the resulting molecules at the H_2-receptor. Thus, the introduction of one nitrogen to produce EATRI yields a molecule that is recognized at the histamine receptor and is also capable of activating it to produce an agonistic response, whereas the introduction of an additional nitrogen to produce EATET yields a molecule that is not recognized at the receptor and is thus inactive, either as an agonist or as an antagonist. The changes in electronic structure and properties of the five-membered ring of EATET relative to histamine prevent the recognition of the former molecule at the receptor. These changes can be analyzed with reference to the limited set of recognition elements identified in our previous work on histamine agonists on the basis of a proposed mechanism for the activation of the receptor (4–6, 11). Those elements were related to the properties of the preferred tautomer of histamine, before its interaction with the receptor, and helped determine the nature of the complementary sites in the receptor: the MEP map of the N(3)-H tautomer, which is considered to be the tautomer of histamine that is recognized at the receptor, revealed near the N(1) of histamine a minimum that could represent a site complementary to a proton-donor site in the receptor; the hydrogen on N(3) could simultaneously be involved in a hydrogen bond at a proton-acceptor site of the receptor. As we showed with other histamine analogs (6), the analysis of a variety of five-membered heterocyclic compounds and of their compatibility with the proposed mechanisms for receptor recognition and receptor activation offers an opportunity to probe the validity of the hypotheses and to elucidate other elements of the process of agonist-receptor interaction.

Computational Methods

Ab initio molecular orbital calculations, including geometry optimization based on analytical calculation of the first derivatives of the energy with respect to coordinates at the Hartree-Fock level (12), were carried out as previously described for histamine (5) and derivatives (6) with the GAUSSIAN 80 systems of programs (13) and the STO-3G basis set (14). Detailed analyses and comparisons summarized in a recent compendium (15) indicate that, for the type of molecules studied here, geometry optimization with this basis set should reliably reproduce the essential structural features. However, for reasons described in detail elsewhere (16, 18), the MEP maps for the compounds in the geometries optimized with the STO-3G basis set were calculated from wave functions obtained with the CHF method (19) and the LP-3G minimal basis set (17). A detailed analysis of the significance and use of MEPs for similar problems showed (20) that the energy-optimized LP-3G minimal basis set defined earlier provides an accurate description of molecular properties that depend on a good representation of the atomic core (16, 17). Moreover, this basis set performed very well in comparison to much more extended basis sets in describing charge redistributions due to molecular interactions (18).

The maps were calculated in the planes of the ring portion of the monocationic forms, protonated at the side chain amine as described previously in detail for histamine derivatives (5, 6) and also for other pharmacologically active compounds (9, 20, 21).

Results and Discussion

Determinants for recognition. Calculations of the structures and energies of the tautomeric forms of the compounds and their properties were used to enable the comparisons of these molecules with histamine and its congeners that are active at the H_2-receptor. The guiding assumption is that the cationic form of the tautomer that matches the histamine N(3)-H tautomer template will be recognized by the receptor (1, 5–8).

The calculated energies of the cationic tautomers of EATRI and EATET are listed in Tables 1 and 2, respectively. The N(1)-H tautomer of the cationic form of EATRI has the lowest energy and is more stable than the N(2)-H and the N(4)-H tautomers by 5.8 and 8.5 kcal/mol, respectively (Table 1). Between the two possible cations of EATET we find that the N(2)-H tautomer is more stable than the N(1)-H tautomer by 5.0 kcal/mol (Table 2). Similar results are obtained with the LP-3G basis set in the STO-3G optimized geometries [results from single point calculations for geometries optimized in a different basis set are given according to the notation of Curtiss *et al.* (22)]. Both tautomers, i.e., the N(1)-H of EATRI (Fig. 1, **1**) and the N(2)-H of EATET (Fig. 1, **5**) correspond structurally to the N(3)-H tautomer of the histamine cation (Fig. 1, **7**) that constitutes the template for recognition by the H_2-receptor (1, 4–8).

The MEP maps of the lowest energy tautomers of the cations of EATRI and EATET are shown in Figs. 2 and 3, respectively. Comparison of the MEP of the N(1)-H tautomer of EATRI (Fig. 2) to that of the N(3)-H tautomer of histamine (Fig. 1a of Ref. 5) reveals a remarkable similarity both in the general shape and in the values of the minima near N(4) of EATRI (Fig. 2) and near N(1) of histamine. These are the equivalent atoms in the receptor recognition of the two molecules (4, 11). The major difference between the two MEP maps is in the region near N(2) of EATRI which corresponds to the region near C(4) of histamine: in histamine this region is clearly

TABLE 1

Total energies (in hartrees) and relative energies (in kcal/mol) for EATRI[a]

Species	Energy		
	N(1)-H	N(2)-H	N(4)-H
Cation			
STO-3G//STO-3G[b]	−369.657372	−369.648168	−369.643700
	0.0	5.8	8.5
LP-3G//STO-3G	−65.060941	−65.053072	−65.047932
	0.0	4.9	8.2
Neutral			
STO-3G//STO-3G	−369.218274	−369.220168	−369.213661
	0.0	−1.2	2.9
LP-3G//STO-3G	−64.655559	−64.659097	−64.650573
	0.0	−2.2	3.3

[a] Relative energies are calculated with respect to the N(1)-H tautomer that is recognized at the H_2-receptor (see text).
[b] Notation according to Ref. 22: LP-3G//STO-3G means single point calculation using LP-3G basis set in the STO-3G optimized geometry.

TABLE 2

Total energies (in hartrees) and relative energies (in kcal/mol) for EATET

Species	Energy	
	N(2)-H	N(1)-H
Cation		
STO-3G//STO-3G[b]	−385.382592	−385.374498
	0.0	5.0
LP-3G//STO-3G	−68.640157	−68.631192
	0.0	5.6
Neutral		
STO-3G//STO-3G	−384.951999	−384.953630
	0.0	1.0
LP-3G//STO-3G	−68.244940	−68.245735
	0.0	0.5

[a] Relative energies are calculated with respect to the N(2)-H tautomer.
[b] Notation as in Table 1.

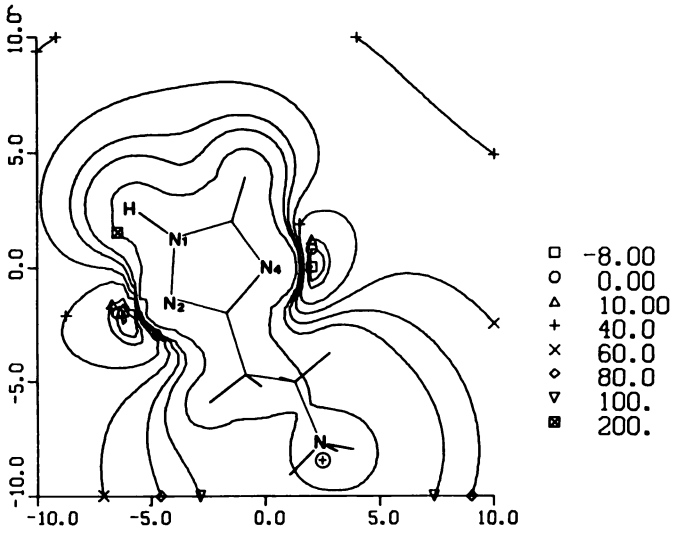

Fig. 2. MEP map (in kcal/mol) for the N(1)-H tautomer of EATRI monocation. The potential in the plane of the triazole portion of the molecule was calculated from the molecular wave function obtained from a pseudopotential calculation (CHF) with the minimal LP-3G basis set.

positive, whereas the region near N(2) in the EATRI is negative with shape and values similar to those near the N(4) atom. A 180° rotation of the five-membered ring of EATRI around the exocyclic bond produces a conformational isomer of the N(1)H tautomer with the N(1)-H bond now occupying the position of N(3)-H in histamine, and a MEP map that is very similar to that of the original conformer. It follows that if one rotamer is recognized at the receptor, the other one would also fit. The similarity of the MEP maps of the conformational isomers of EATRI is due to the positioning of the C(5)-H bond of the rotated conformation in the same place as the N(1)-H bond in the original conformation. However, these two bonds have different properties and may not be able to serve similar functions in the process of recognition. For example, the N(1)-H bond is more polar than the C(5)-H, a difference which is nearly imperceptible in the strongly positive region of the MEP map. However, a few per cent difference in the electrostatic interaction of 80–100 kcal/mol would result in a stronger interaction of the NH than of the CH bond with a proton acceptor site on the receptor (see Refs. 4 and 11, and below). Based on the difference in the electronic structure of a C-H bond compared to the N-H bond and the ability of the latter to fit directly the proposed recognition model (4, 11), we conclude that the original, non-rotated conformation will contribute to recognition. It is also reassuring that this conformation is somewhat lower in energy (1.3 kcal/mol) than the rotated conformation.

These considerations and their correspondence with the recognition model proposed before (4, 11) serve to establish an hypothesis that refines the recognition criteria of five-membered heterocycles. It pertains to the region near the N(2) area of EATRI which corresponds to the C(4) area in histamine. Because the MEP near N(2) of EATRI is negative whereas the corresponding area near C(4) of histamine is positive, and yet EATRI is recognized at the H_2-receptor, we must conclude that the receptor has no selectivity with respect to the electrostatic properties near this position. This lack of selectivity is consistent also with the known lack of steric constraints in this position, as can be seen, for example, in drugs that have bulky and electronically different substitutions at the C(4) position

of histamine, e.g., the selective H_2-agonist 4-methyl histamine (1–3, 6–8).

Comparison of the MEP of the N(2)-H tautomer of the cation of EATET (Fig. 3) to that of EATRI (Fig. 2) and of histamine (cf. Fig. 1a of Ref. 5) shows major differences both in the shape of the MEP and in its values. First, the MEP of EATET, unlike that of histamine, has multiple local minima of which the major one is positioned near N(3), which corresponds to C(2) in histamine. Second, this is also the only negative local minimum, for the other two near the N(1) and N(4) positions of EATET are positive. EATET lacks, therefore, the important recognition element identified earlier (4, 11) in the form of a negative electrostatic potential that is to be found near N(1) of histamine and near N(4) of EATRI. These differences in the MEP of EATET compared to histamine and EATRI explain why EATET cannot be recognized at the H_2-receptor and are thus responsible for the inactivity of EATET at that receptor.

The analysis presented above demonstrates how introduction of one nitrogen into the imidazole ring to produce the 1,2,4-triazole may not disturb the electrostatic potential of the ring sufficiently to prevent its recognition at the H_2-receptor, whereas the introduction of one more nitrogen to form the 1,2,3,4-tetrazole ring could make recognition impossible. These effects of modifications in the imidazole portion are explained by the nature of the changes produced in the pattern of the electrostatic potentials surrounding the five-membered rings. In particular, the comparisons suggest that the negative electrostatic potential near N(3) of EATET, which is positioned where the potential is positive near the C(2) of histamine, plays a crucial role in the prevention of recognition of EATET by the histamine-H_2 receptor.

Determinants for activation. The initiation of receptor activation to trigger a response is dependent on the successful recognition of the agonist by the receptor and the formation of an agonist-receptor complex (9, 10). It is therefore clear that because EATET is not recognized by the receptor it would not form the drug-receptor complex and will not be able to activate it. Consequently, our discussion of the activation of the histamine H_2-receptor is limited to EATRI and its molecular properties that are responsible for this process.

An activation mechanism of H_2-receptor was previously proposed based on the changes in the tautomeric preference of histamine that occur as a consequence of the neutralization of the side chain (4, 11). According to this mechanism, the N(3)-H tautomer, which is the more stable cationic form, is recognized at the receptor. Upon neutralization of the side chain due to interaction with a negatively charged site in the receptor, the tautomeric preference changes to increase the population of the N(1)-H form.

This change in tautomeric preference triggers a proton transfer in the agonist-receptor complex through the imidazole portion of histamine. As a consequence of the recognition and binding of histamine at the receptor, a proton moves from the proton-donor site interacting with N(1) to the proton acceptor site interacting with N(3)-H. A detailed description of the receptor recognition process that takes into account the correct molecular determinants for activation was obtained recently from our computational simulation of the mechanism of proton transfer in a model of the histamine-H_2 receptor (11). The simulation of the proton transfer process sustained by histamine (11) was carried out for a sequential mechanism, i.e., a transfer of the proton from the proton-donor on the receptor to N(1) of histamine followed, under certain circumstances, by the transfer of a proton from N(3) of the protonated histamine to the proton acceptor in the receptor model. We showed that the transfer of the proton from the receptor model to the imidazole ring of the agonist is the trigger for the simulated process of activation. In accordance with this conclusion, the relevant EATRI species to be considered in the model for receptor activation are the three tautomers in which the side chain is neutralized and the triazole ring is protonated, thus simulating the results of the interaction with an anionic site I and the acceptance of the proton from site III of the receptor model (see Fig. 4, and Fig. 1 of Ref. 11).

The energies of the three possible forms of EATRI that have captured a proton from the proton-donor site and are protonated on the 1,2,4-triazole ring are shown in Table 3. The

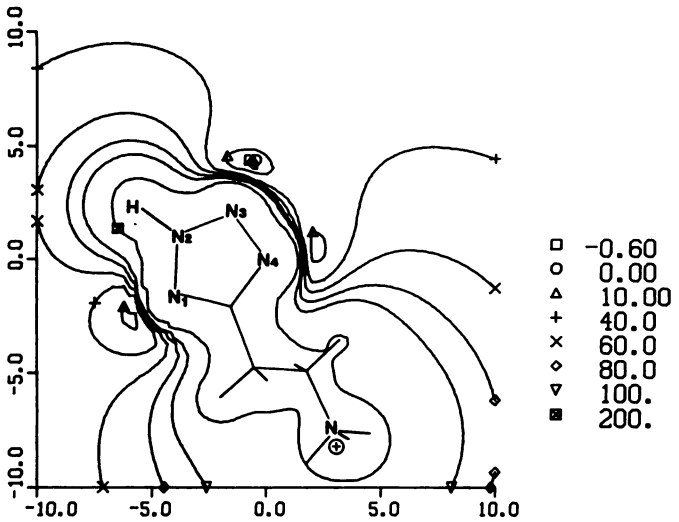

Fig. 3. MEP map (in kcal/mol) for the N(2)-H tautomer of EATET monocation. The potential in the plane of the tetrazole portion of the molecule was calculated from the molecular wave function obtained from a pseudopotential calculation (CHF) with the LP-3G minimal basis set.

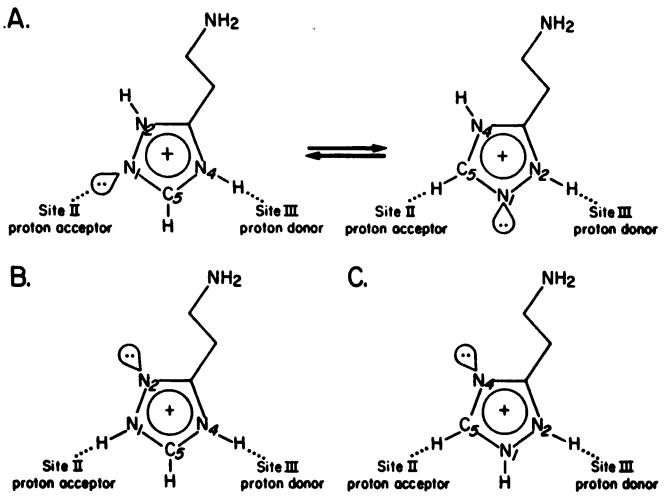

Fig. 4. Schematic representation of potential modes of interaction of EATRI tautomers with sites II and III of the receptor model defined in Refs. 4 and 11. The tautomers are shown after the first step in the mechanism in which they have captured a proton from the proton donor site.

TABLE 3

Total energies (in hartrees) and relative energies (in kcal/mol) for the ring protonated isomers of EATRI

Computational Level*	Energy		
	N(1)-H, N(2)-H	N(1)-H, N(4)-H	N(2)-H, N(4)-H
STO-3G//STO-3G	−369.630872 18.8	−369.653614 4.5	−369.660840 0.0

* Notation as in Table 1.

interactions of the possible forms of EATRI with a receptor model in which the proton from site III was transferred to the ring are shown in Fig. 4. The lowest energy isomer (Table 3) is the one protonated on the N(2) and the N(4) atoms (the N_2N_4 cation). According to the determinants for recognition presented in the previous section, this form cannot be responsible for the activity of EATRI because it cannot be recognized by the receptor. The inadequate fit is demonstrated in Fig. 4A, in which two possible conformations of the N_2N_4 cation are shown interacting with the receptor model. The figure explains why neither of these conformations is likely to have an energetically favorable interaction with the receptor: according to the structure on the left, the lone pair of N(1) is facing site II, the proton acceptor site, so that the repulsion between these two groups with high charge densities will prevent a stable interaction. In the scheme on the right, two other structural factors will affect the stability of the complex: one is that the high electron density of the lone pair of N(1) which generates a negative potential would be placed in a position equivalent to C(2)-H of histamine at which the receptor requires a positive potential, as shown by the analysis of EATET (see above). The other is that the C(5)-H bond is required to mimic an N-H bond which it cannot do successfully, as explained above for the rotational conformer of EATRI. This N_2N_4 cation is therefore not likely to play a role in the activity of EATRI.

For the two remaining isomers, the N_1N_4 and N_1N_2 cations, Fig. 4B demonstrates that the N_1N_4 tautomer can both be recognized by the receptor and activate it whereas, for the N_1N_2, the interaction would be unfavorable (Fig. 4C). As shown in Fig. 4B, the favorable interaction of N_1N_4 is due to the fact that it juxtaposes perfectly the N(1)-H part of the triazole ring to the negatively charged proton acceptor site II and prepares N(4) to accept a proton from the proton-donor site III. The relative energy of the other isomer, the N_1N_2 cation, is 14.3 kcal/mol above that of the N_1N_4 cation, and its simulated interaction with the receptor model shown in Fig. 4C illustrates why the arrangement would be unfavorable, in full agreement with our conclusion that the rotated form of the N(1)-H tautomer will not be recognized by the receptor (see above). We conclude that of all the possible tautomeric forms of EATRI the molecule will be recognized as the N(1)-H tautomer and will be able to start the activation of the receptor by accepting a proton on N(4).

Conclusions

The analysis of the relative energies and the MEP maps of the various tautomers of EATRI and EATET provides an explanation for their different activities on the H_2-receptor that is consistent with the mechanisms proposed for histamine. By identifying the specific reasons for the inactivity of EATET in the molecular properties that prevent its recognition by the receptor, we obtain a more stringent definition of the molecular determinants for recognition at the H_2-receptor than was available before from the analysis of histamine and other imidazole derivatives. When these stringent recognition criteria were applied to the ring-protonated isomers of EATRI as a discriminating first step in the receptor interaction, we were able to explain the activity of this molecule, to identify the active isomer (N_1N_4), and to outline a specific hypothesis for the sequence of the activation mechanism starting with protonation at N(4). These conclusions and the refinement of the discriminant molecular determinants for receptor recognition [e.g., the incompatibility with the negative region near C(2)] and activation (e.g, the nature of groups admissible at site III) are essential for reliable descriptions of agonist and antagonist interactions at the histamine H_2-receptor. Because they are based on molecular properties rather than on the chemical identity of the functional groups, these conclusions are generalizable to structures other than imidazole derivatives and to other congeners with five-membered rings.

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