32, 91587-18-7; 33, 4486-29-7; 34, 4228-39-1; (E)-35, 91587-20-1; 36, 91587-21-2; 37, 91587-22-3; 38, 91780-92-6; 39, 91587-23-4; 40, 91587-24-5; 41 (X = O), 108-95-2; 41 (X = S), 108-98-5; 42 (X = O), 54897-52-8; 42 (X = S), 70030-51-2; 43 (X = O), 29598-22-9; 43 (X = S), 91587-25-6; 44 (X = O), 40614-20-8; 44 (X = S), 91587-26-7; 45, 10276-04-7; 46 (X = O), 40614-27-5; 46 (X = S), 66165-06-8; 47 (X = O), 88579-19-5; 47 (X = S), 88579-23-1; 48 (X = O), 88579-28-6; 48 (X = S), 88579-35-5; 49, 68837-59-2; 50, 91587-27-8; 51, 2408-37-9; 52, 91587-28-9; 53, 91587-29-0; 54, 41891-54-7; 55, 91587-30-3; 56, 91587-31-4; 57, 84337-86-0; 58, 91587-32-5; 59, 91587-33-6; 60, 91587-34-7; $(C_6H_5O)_2POCl$, 2524-64-3; $Me_2C{=}CHCH_2Br$, 870-63-3; ethyl 3-(bromomethyl)-benzoate, 62290-17-9; 1,4-methano-1,4-dihydronaphthalene, 4453-90-1; 3-methyl-3-buten-1-ol, 763-32-6; diphenyl 3-methyl-3-buten-1-yl phosphate, 42007-25-0; 4-bromo-2-methylbenzaldehyde, 24078-12-4; 4-(1-hydroxy-2,2,6-trimethylcyclohexyl)-2-methylbenzaldehyde, 91587-35-8; 4-(4-bromophenyl)toluene, 50670-49-0; vitamin A, 11103-57-4; acetone, 67-64-1.

Notes

A Theoretical Investigation of Histamine Tautomerism

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Geometry optimizations of the structures of histamine (neutral and monocation) in the N(3)-H and N(1)-H tautomeric forms were performed at the ab initio Hartree–Fock level with the STO-3G basis set. Values of the structural parameters and their changes upon protonation and/or tautomerization are in good agreement with data from X-ray crystal-structure analysis of histamine and several analogues. Earlier predictions of the tautomeric preference from calculations using frozen geometries based on crystal-structure data are confirmed by calculations of energies of histamine in the fully optimized geometries with both the STO-3G and LP-3G basis sets and by comparisons of the minima in the molecular electrostatic potentials of the two tautomers. These results support a previously proposed model for the activation of the histamine H_2 receptor.

There are two possible tautomers of the imidazole ring of histamine in both the neutral (free base) and the cationic (protonated at the side-chain nitrogen) forms. In the N(3)-H tautomer the N(3) nitrogen of the imidazole ring of histamine bears a hydrogen while the N(1) nitrogen does not; this is reversed in the N(1)-H tautomer. In the crystal of the cation[1] only the N(3)-H tautomer is found, whereas the N(1)-H tautomer is found when the neutral species is crystallized.[2] In aqueous solutions the N(3)-H form is predominant at both acidic and basic pH, but the relative ratio of the N(3)-H to N(1)-H forms is much greater when histamine monocation is the main species in solution.[3] Ab initio quantum chemical calculations of the various forms of the histamine molecule kept in frozen geometries show the same preference of the N(3)-H form over the N(1)-H form as a function of the protonation state of the side chain.[5,7] The evidence from structure–activity relationships showing that imidazole ring tautomerism is required for activity at the H_2 receptor[4] led to a proposed mechanistic model describing the possible involvement of the change in the proton affinity of the imidazole nitrogen as a function of side-chain protonation in the activation of the receptor.[5] In this model, histamine, which is predominantly in the cationic form at physiological pH, is assumed to approach the receptor as the N(3)-H tautomer. The cationic side chain interacts with a negative region of the receptor. As the side chain is anchored, the neutralization causes a shift in the tautomeric preference to N(1)-H. N(1) could then attract a proton from a proton-donor site on the receptor while N(3) could act as a proton donor for a proton-acceptor site. Thus the change in the tautomeric preference induced by the neutralization of the side chain leads to a proton-relay process at the receptor[5].

This hypothesis was explored with ab initio quantum chemical calculations of the neutral and cationic forms of histamine in the N(1)-H and N(3)-H tautomeric forms.[5] The calculations were done with the Whitman–Hornback basis set, with histamine in the geometries taken from crystallographic data for the cation and the free base. Thus, geometries of the four possible species shown in Scheme I were modeled[5,6] by the crystal structures of 1 and 4 only. The results provided the basis for the proposed mechanism which depends on the change in tautomeric preference from nearly full N(3)-H preference to a higher probability for the N(1)-H tautomer when the cation is neutralized.

The theoretical conclusions on the difference in tautomeric preference between the free base and the monocation of histamine were found to be unchanged for several choices of the geometry of the imidazole ring. Attempts to improve on these approximations[7] in order to construct better frozen geometries for the species for which the crystal structures are not available, i.e., 2 and 3, also did not change the conclusions about the tautomeric preferences; nevertheless, the question of the best geometry to be chosen for these calculations remained open.[7] We report here on the effect that full geometry optimization has on the conclusions regarding the tautomeric preference in the four structures in Scheme I.

Methods

In order to obtain reliable structures for all four species

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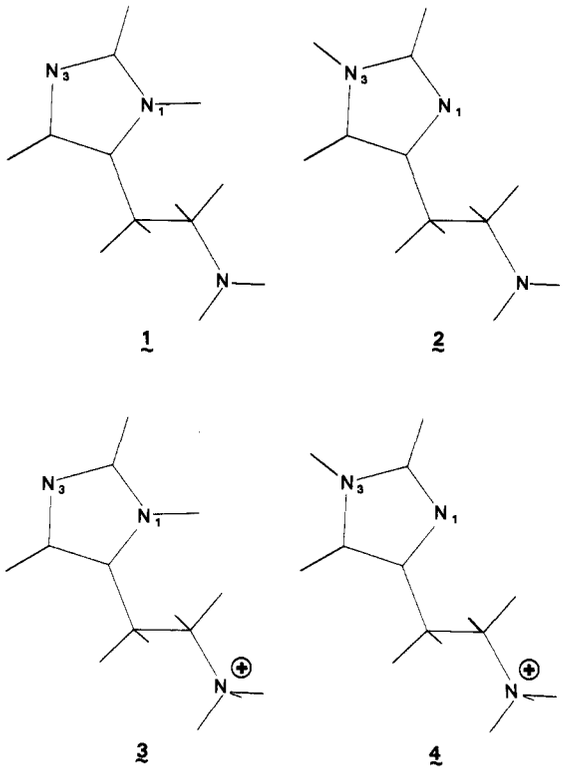
Table I. Optimized Values of the Imidazole Ring Parameters and Side-Chain Dihedral Angles of the Histamine Tautomers Shown in Scheme I

structural parameter	N(1)-H tautomer		N(3)-H tautomer	
	neutral 1	cation 2	neutral 3	cation 4
	Angle (degrees)			
$C_4C_5N_1$	105.2	105.6	110.5	111.2
$C_5N_1C_2$	107.0	106.4	104.7	104.4
$N_1C_2N_3$	111.9	112.1	112.1	111.8
$C_2N_3C_4$	104.3	104.4	106.4	106.9
$N_3C_4C_5$	111.7	111.5	106.3	105.7
τ_1	75.2	99.5	58.7	39.8
τ_2	183.8	175.6	182.2	191.1
	Bond Length (Å)			
C_5N_1	1.395	1.396	1.416	1.409
N_1C_2	1.385	1.383	1.314	1.317
C_2N_3	1.315	1.318	1.383	1.382
N_3C_4	1.410	1.406	1.393	1.387
C_4C_5	1.351	1.351	1.349	1.350

Scheme I



(Scheme I) and to investigate the possible effect on the mechanistic conclusions from the calculations, we performed optimizations of the molecular geometries. These include the conformation of the side chain (keeping the imidazole portion planar) for the N(1)-H and N(3)-H neutral and cationic species. Energies and molecular properties were calculated with different basis sets. The STO-3G basis set[8] was used with the GAUSSIAN 80 system of programs.[9] In the optimization of the N(3)-H cation we observed a tendency for the end of the side chain to twist toward the ring so as to form an internal hydrogen bond between N(1) and a proton of the protonated amine. In our model for the interaction of histamine with the H_2 receptor,[5] this geometry is irrelevant and was therefore avoided in the calculations. The molecular electrostatic potentials (MEP) were then calculated as described before[10,11] with wave functions obtained with the coreless Hartree–Fock (CHF) pseudopotential[12] and the LP-3G basis set. The LP-3G basis set is a valence-only minimal basis set which has been optimized to give the lowest atomic energy when used in a CHF pseudopotential calculation of the ground state of the atom.[13] It appears to be a reliable predictor of properties dependent on charge distribution,[16] e.g., MEP.

Results and Discussion

A. Structural Parameters. Table I contains the final parameters defining the imidazole ring and the dihedral angles of the side chain (τ_1, and τ_2) obtained from the complete geometry optimization of the four species in Scheme I. Comparison with data from X-ray crystallography tabulated by Richards et al.[7] shows an excellent agreement between the optimized structural parameters obtained here (Table I) and those obtained experimentally for histamine and several related compounds. Notably, both our results and the experimental data show that the parameters of the imidazole ring structure are much more sensitive to the tautomeric form (i.e., N(1)-H vs. N(3)-H) than to the state of protonation of the side chain. For example, the value of the angle $C_4C_5N_1$ is 5.0° larger for the N(3)-H (cation or neutral) than for the N(1)-H tautomer but differs by less than 0.5° between the cation and the neutral species of the same tautomer. Similarly, the angle $C_5N_1C_2$ changes very little on protonation of either neutral tautomer but decreases by 2.0° upon tautomerization from N(1)-H to N(3)-H. The other ring angles change in a parallel fashion: $N_3C_4C_5$ decreases by 5.0° when going from the N(1)-H tautomers (cation or neutral) to the N(3)-H tautomers, corresponding to the increase in the $C_4C_5N_1$ angle, but changes only slightly upon protonation. Angle $C_2N_3C_4$ increases by 2.0°, corresponding to the 2.0° decrease of angle $C_5N_1C_2$ when going from the N(1)-H to the N(3)-H species, but the $N_1C_2N_3$ angle between N(1) and N(3) does not change significantly upon tautomerization or protonation.

The same trends for the changes in angles are found by X-ray crystallography for histamine analogues in the N(1)-H and N(3)-H tautomers.[7] For example, angle $C_4C_5N_1$ is 4.5° smaller for histamine base, which crystallizes as the N(1)-H tautomer, than for histamine hydrobromide, which crystallizes as the N(3)-H tautomer.[7] Similar agreement for the other ring angles is obtained for the other compounds tabulated by Richards et al.,[7] including 6-histaminopurine, L-histidine, cyclo(L-threonyl-L-histidyl) dihydrate, the H_2-antagonists burimamide, thiaburimamide, and metiamide (all N(3)-H tautomers), as well as imidazole. The changes of bond lengths in the imidazole ring

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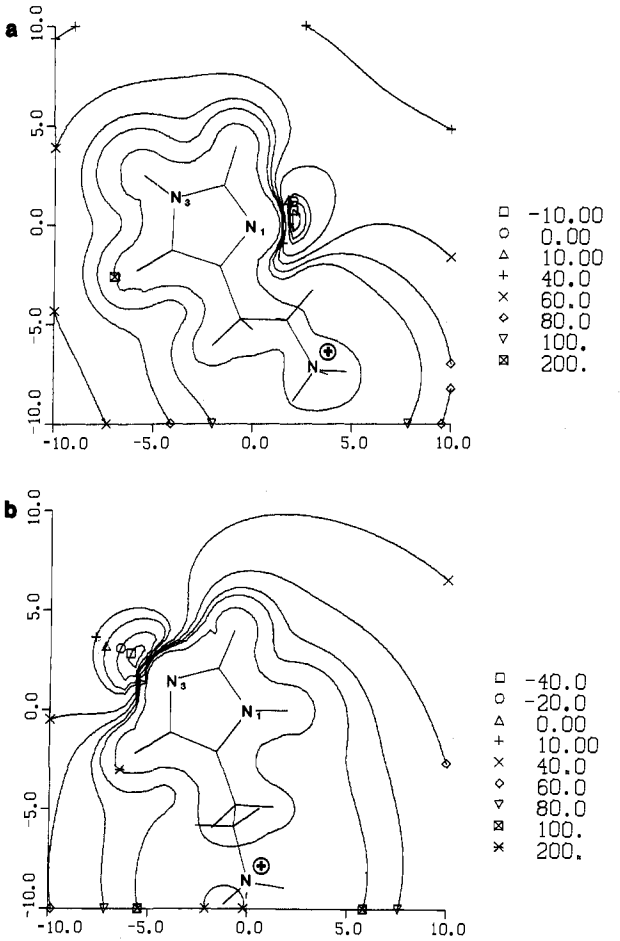

Figure 1. Molecular electrostatic potential map (values given in kcal/mol) in the plane of the imidazole ring of histamine tautomers calculated with the LP-3G basis set at the STO-3G optimized geometry: (a) the cation N(3)-H, (b) the cation N(1)-H.

are analogous to the changes in angles described above. Thus, the decrease in N_1C_2 by about 0.065 A° upon going from the N(1)-H to the N(3)-H tautomer is accompanied by the increase in C_2N_3 and corresponds to the decrease in the angle $N_3C_4C_5$. Again, side-chain protonation does not induce such large changes. Similarly the bond lengths C_5N_1 and N_3C_4 change in opposite directions by similar amounts upon tautomerization, while C_4C_5 (corresponding to the angle $N_1C_2N_3$) remains unchanged. Finally, the dihedral angles of the side chain show only small variation from the values of the fully extended geometry ($\tau_1 = 90°$, $\tau_2 = 180°$). Thus τ_2 is always within 15° of 180°; τ_1 tends to be closer to 90° for the N(1)-H tautomers than for the N(3)-H tautomers, probably due to steric repulsion between the side chain and the hydrogen on N(1) in the N(1)-H tautomer.

B. Inferences for the Model of Histamine H_2 Receptor Activation. The energies, the molecular properties, and the rearrangements that lead to the previously proposed model for activation of the histamine H_2 receptor[5] are supported by the results of the extended calculations reported here. This can be seen both in the MEP and in the energies of these systems. The salient feature of the MEPs shown in Figure 1 are the highly localized

Table II. Stabilization Energies of Histamine Tautomers in Geometries Optimized with the STO-3G Basis Set

histamine species	ΔE,[a] kcal/mol	
	STO-3G	LP-3G
cation	−10.44	−9.81
neutral	0.99	1.80

[a] Defined as the difference in the total molecular energy of the N(3)-H and N(1)-H tautomers ($\Delta E = E_{N(3)-H} - E_{N(1)-H}$).

minima in the vicinity of the unprotonated ring nitrogen (N(1) in the N(3)-H tautomer and vice versa) and the positive potential surrounding the rest of the molecule. The value of the MEP at each point is the interaction energy between the molecule and a positive point charge and, therefore, represents a first approximation to the interaction with a proton.[11] The location of the minimum is indicative of the site of protonation, and the relative values of the minima (cf. Figures 1a and 1b) are indicative of the relative proton affinity.[5,11] Thus, the general pattern of the MEP in the plane of the imidazole ring of the N(1)-H and N(3)-H cation tautomers with optimized geometries indicates that the N(3) position in the N(1)-H tautomer of the cation has a higher proton affinity than the N(1) position of the N(3)-H tautomer of the cation (Figure 1); the cation is therefore predicted as before[5] to be preferably in the N(3)-H tautomeric form.

Table II shows that both all electron STO-3G calculations and the CHF LP-3G calculations predict the same changes in the tautomeric preferences from the energy differences calculated with the fully optimized geometries. Thus the previous predictions of relative tautomeric preferences[5] do not change when molecular geometries optimized for each species with the STO-3G basis set are used in the ab initio calculations in place of the experimentally derived geometries. Furthermore, the predictions regarding tautomeric preference were not found to be sensitive to the choices of basis sets made here, although the two basis sets used here gave different electron-density redistributions in molecular interactions in other systems.[14] It appears, therefore, that while the cautions presented recently[7] regarding the effect of the unknown environment of the receptor on the mechanistic conclusions may still be relevant, those regarding the effect of the geometry of histamine on the mechanistic conclusions were not. The ability of the mechanistic model to explain H_2-receptor activation by compounds which differ structurally from histamine, e.g., dimaprit, and especially its ability to explain antagonism at the same receptor[3,15] should be explored to further probe its validity.

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Registry No. Histamine, 51-45-6; histamine monocation, 29997-54-4.