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Theoretical Studies on the Activation Mechanism of the Histamine H_2-Receptor: The Proton Transfer between Histamine and a Receptor Model

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SUMMARY

A proposed molecular mechanism for the activation of the H_2-receptor of histamine was simulated with *ab initio* calculations including geometry optimization with several basis sets. The system is modeled by a proton-relay chain produced by the binding of a histamine molecule to a receptor model consisting of an anionic anchoring site, and proton donor and acceptor sites. The anchoring of histamine cation at a negative receptor site is simulated by the interaction with a hydroxyl anion or by calculations on neutral histamine; the proton donor and acceptor sites are modeled by ammonium and ammonia groups, respectively. Results of the calculations reveal that a significant decrease in the barrier for the movement of the proton from the donor site to the N1 nitrogen in the imidazole portion of histamine occurs as a consequence of the neutralization of the side chain and the simultaneous interaction of the N3 nitrogen with the proton acceptor. An increase of the driving force for the proton transfer process is produced by these interactions, as observed from the relative energies of the initial and final steps of the charge relay. The barrier and the driving force depend on the nature of the proton acceptor site. This simulation of the receptor activation mechanism provides the basis for exploration of the partial receptor activation by molecules characterized as partial agonists and the lack of activation by molecules that act as antagonists on this receptor.

From early studies on compounds with HA H_2-receptor activity, it was proposed that tautomerism in the imidazole portion of the HA molecule can be directly involved in the receptor activation mechanism (see Refs. 1 and 2). Experimental evidence as well as structure activity considerations led to the formulation of a mechanistic model for the activation process at the HA H_2-receptor (1). In this model, HA, which is predominantly in the monocationic form at physiological pH (2), is considered to approach the receptor as the N3-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 from N3-H to N1-H. N1 then tends to pick up a proton from a proton donor site on the receptor, while N3 could act as a proton donor for a proton acceptor site with which the HA is interacting. The change in the tautomeric preference induced by the neutralization of the side chain can thus lead to a proton relay process at the receptor to trigger the biological response. This mechanistic hypothesis was previously explored with quantum chemical calculations performed on the tautomeric forms of the HA molecule (1, 3). The results revealed the effect of the ethylamine side chain protonation on the tautomeric equilibrium between N3-H and N1-H, and showed how the structure of the isolated HA molecule varies when protonation (or deprotonation) of the ethylamine side chain occurs. However, the dynamic details of a possible proton relay from one receptor site to the other, mediated by the change induced in proton affinity of the imidazole nitrogens upon anchoring at the anionic site, cannot be revealed by calculations on the agonist alone.

Here we present the results of a study of the energetic profile of such a proton transfer process with emphasis on the parameters for the construction of a more complete HA receptor activation model. Such a model would provide the basis for comparison of various agonists producing the same activation mechanism, and for an exploration of the effect that the molecular environment in the receptor could have on such a process.

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ABBREVIATIONS: HA, histamine.

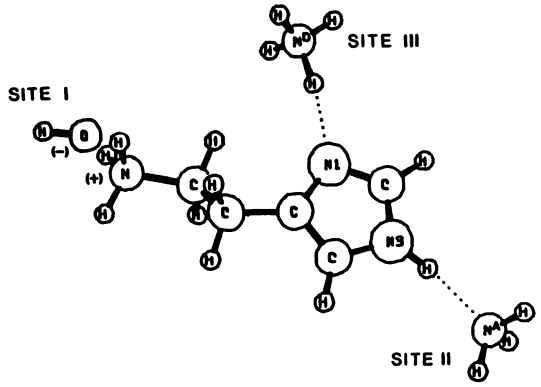

Fig. 1. The proton transfer system: HA N3-H monocation interacting with hydroxyl anion (*SITE I*), ammonia (*SITE II*), and ammonium (*SITE III*). The site numbering refers to the proposed model for the HA H_2-receptor (1).

Computational Details

Methods of calculation. All calculations reported here were performed using a version of the GAUSSIAN 80 package of programs, modified to run on an IBM computer system.[2] The minimal STO-3G basis set, as well as split valence 3-21G, 4-31G, and 6-31G basis sets (4–7) were used for these calculations. Geometry optimizations were performed with the optimization procedures in the GAUSSIAN 80 system of programs that is based on analytical calculation of the first derivatives of the energy at the Hartree-Fock level (8).

Construction of the proton transfer system. As a model system to study the proton transfer process proposed for the activation stage of the HA H_2-receptor, we used the histamine molecule placed between the molecules of ammonia (proton acceptor) and ammonium (proton donor) as shown in Fig. 1. The starting geometry of the system to study the movement of the proton from ammonium (site III) toward the N1 nitrogen of the imidazole ring was optimized at the STO-3G level. During the course of optimization we kept the conformation of the ethylamine side chain in the geometry and conformation obtained previously from the optimization of the N3-H cationic form of HA (3). This choice is based on the conclusion from previous structure-activity studies that this is the form of HA recognized at H_2-receptors (1–3). As discussed previously (9), this constraint is in keeping with the assumption of a relatively rigid receptor recognition site which is supported by both theoretical and experimental studies (10–13) on the pharmacology of the HA H_2-receptor. The optimized structure contains linear hydrogen bonds between N^D and N1 and between N^A and N3 (see Fig. 1) at the optimized distances of 3.07 and 2.90 Å, respectively. The coordinates of the model are listed in the Appendix. Potential energy curves for the movement of the proton from site III toward the N1 nitrogen were obtained by fitting fifth order polynomials to points calculated at each position of the moving proton with full reoptimization of the ammonium/imidazole/ammonia portion of the model with the exception of the N^D to N^A distance which was kept frozen at 7.91 Å. The same assumptions and procedures were followed in the exploration of the movement of the proton away from the N3 position toward site II. Due to the fitting procedure, the energy values reported in Tables 1–3 bear an error of ±0.5 kcal/mol.[3]

Results and Discussion

Proton transfer from site III to N1. The potential energy curves for the proton movement from the proton donor site (site III in Fig. 1) toward the N1 nitrogen of the N3-H tautomer of HA are shown in Fig. 2. The H . . . N3 distance was kept fixed at 1.0 Å. The movement of the proton toward N1 results in energy changes from Min 1, which corresponds to the proton being near the model receptor site III, to Min 2, which corresponds to the proton being near the N1 nitrogen. In the HA cation, the driving force for this movement, calculated as the difference between Min 1 and Min 2, is 15.8 kcal—the "stabilization energy" in Table 1. The barrier to the movement is calculated from the corresponding energies at Min 1 and at Max to be 15.3 kcal/mol (Table 1). The minimum energy at Min 2 is reached when the proton approaches the N1 nitrogen atom to a distance of 1.07 Å. The other minimum on the potential energy curve (Min 1) corresponds to a situation in which the proton is bound to the ammonia molecule with an internuclear H-N distance of 1.10 Å.

Neutralization of the ethylamine side chain, simulated by calculations of HA with the neutral (free base) form of the ethylamine side chain, leads to a lowering of the barrier by nearly 4 kcal/mol to 11.5 kcal/mol, and an increase of the driving force to 20.6 kcal/mol (see Fig. 2 and line IV of Table 1).

The use of the nonprotonated side chain (free base) species as a model for the cationic molecule neutralized at a negatively charged receptor site has previously been described in the theoretical studies of histamine (1–3, 9) and 5-hydroxytryptamine analogs (14–16). It was shown that molecular properties such as the pattern of the molecular electrostatic potential are similar for the free base and the neutralized form of the molecule. To estimate how this approximation can affect our findings on the height of the barrier and the driving force to proton transfer, we performed single point *ab initio* calculations for the system shown in Fig. 1 with a hydroxyl anion at various distances from the side chain amine nitrogen. Results summarized in Table 2 show that the driving force for the proton transfer from site III to N1 increases, and the barrier decreases as the OH^-—a model of the negatively charged receptor site (site I)—approaches the ethylamine side chain of histamine monocation. Results in Fig. 2 demonstrate that the potential energy curve obtained from calculations with the distance of 2.19 Å between the hydroxyl anion and the side chain nitrogen

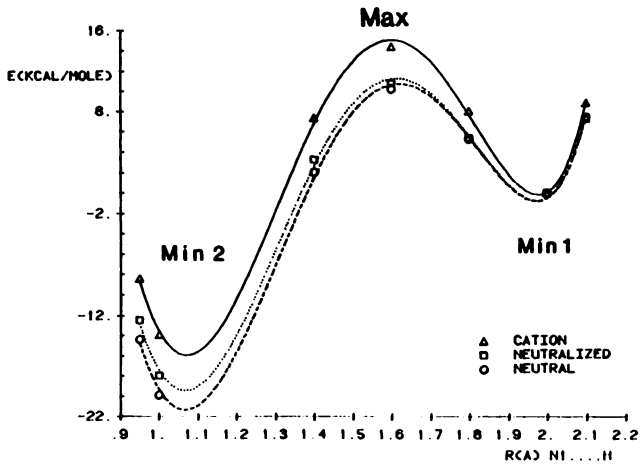

Fig. 2. Potential energy curves for proton transfer from site III to N1, calculated with the STO-3G basis set for: △, HA N3-H monocation; □, neutralized HA N3-H monocation (H_3N^+ . . . . OH^- distance is 2.19 Å); and ○, neutral HA N3-H.

[2] Binkley, J. S., R. A. Whiteside, R. Krishnan, R. Seeger, D. J. De Frees, H. B. Schlegel, S. Topiol, L. R. Kahn, and J. A. Pople. GAUSSIAN 80, IBM version (unpublished).

[3] The equations obtained from the fitting procedure are available from the authors upon request.

TABLE 1
Barriers and stabilization energies for proton transfer calculated with the STO-3G basis set

HA species	Proton transfer from site III to N1 of the N3-H tautomer of HA[a]			
	Site II	Energy barrier	Stabilization energy	Total energy[b]
			kcal/mol	*hartrees*
I. Cation		18.9	9.1	−409.725926
II. Neutralized cation[c]		15.4	12.1	−484.249727
III. Cation	NH_3	15.3	15.8	−465.223086
IV. Neutral	NH_3	11.5	20.6	−464.883456
V. Neutralized cation[c]	NH_3	12.1	18.7	−539.740968
VI. Cation	OH^-	5.5	36.3	−484.065096
VII. Neutralized cation[c]	OH^-	3.9	39.2	−558.521924
	Proton transfer from N3 to site II of the N1-H tautomer			
	Site III	Energy barrier	Stabilization energy	
			kcal/mol	
VIII. Neutral	NH_3	16.2	−14.8	

[a] For numbering scheme see Fig. 1.
[b] Values are for N3. . . H and N1. . . H distances of 1.0Å. Total energies of the components (in hartrees) are: i) neutralizing hydroxyl ion: −74.060300; ii) ammonia in site II: −55.455417; and iii) hydroxyl in site II: −74.064094.
[c] $H_3N^+ \ldots OH^-$ distance of 2.19Å

TABLE 2
Dependence of barriers and stabilization energies for proton transfer from site III to N1 on the side chain $H_3N^+ \ldots OH^-$ distance calculated with the STO-3G basis set for the model in Fig. 1

$H_3N^+ \ldots OH^-$ distance[a]	Energy barrier	Stabilization energy	Total energy[b]
Å		*kcal/mol*	*hartrees*
3.00	13.9	15.1	−539.594023
2.85	13.6	15.7	−539.624630
2.75	13.3	16.1	−539.646553
2.19	12.1	18.7	−539.740968

[a] At each distance the potential energy curve for proton transfer was calculated from the optimized geometry of the complex of neutral histamine with the proton acceptor and donor at sites II and III.
[b] Values are for N3. . . H and N1. . . H distances of 1.0Å. The O-H distance in the hydroxyl is 0.9893 Å; the H-O-N angle between the hydroxyl and the amine nitrogen is 100.1°; the O-N-C_α angle is 111.4°; and the dihedral angle H-O-N-C_α is 180°.

closely follows that calculated with the neutral molecule. The distance of 2.19 Å between the side chain NH_3^+ and the OH^- is also the optimal interaction distance between NH_4^+ and OH^- calculated with the STO-3G basis set (distances of 2.33 and 2.32 Å were obtained from optimization with the split valence 3-21G and 6-31G basis sets). Consequently, the last entry in Table 2 represents the energetics of the proton transfer for an HA molecule anchored at an anionic receptor site.

Basis set dependence of the potential energy curve for proton transfer from site III. To probe the basis set dependence of the results from the simulation, we defined the truncated model shown in Fig. 3, for which we were able to perform *ab initio* calculations with larger, split valence basis sets. The 5-methylimidazole placed between ammonia and ammonium molecules is a system that can reproduce the proton transfer process in the imidazole portion of the neutral HA molecule and is also small enough to permit full geometry optimization with both the STO-3G and the split valence 3-21G basis sets. Results from STO-3G and 3-21G calculations on that model, along with single point 4-31G and 6-31G calculations at the 3-21G optimized geometries, are given in Table 3. The double well shape of the potential curves is reproduced with all basis sets (Fig. 4). The barrier to proton transfer calculated with STO-3G basis set is 10.3 kcal/mol, whereas the 3-21G calculation yields 9.6 kcal/mol. Calculations with 4-31G and 6-31G basis sets at the 3-21G optimized geometries yield values of the barriers and the driving force that differ only slightly when the quality of basis set improves. The effect of basis set extension and correlation energy on the parameters

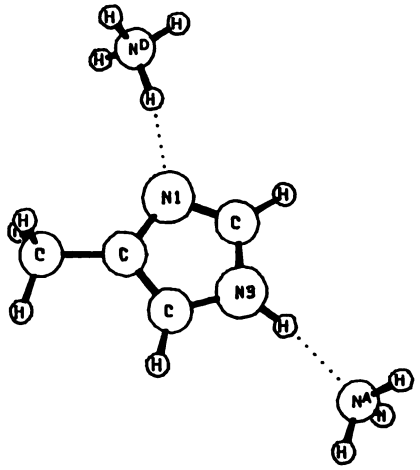

Fig. 3. The reduced model of the proton transfer system used in calculations with various basis sets.

of the potential energy curve for proton transfer has been investigated by Scheiner and co-workers (17, 18), who showed that these improvements in the level of accuracy of the calculations have opposite effects on barrier heights. The results obtained for proton transfer processes similar to the ones described here led to the conclusion that a split valence basis set of the kind used here benefits from a cancellation of errors that render it satisfactory for the description of these proton transfer processes (19).

TABLE 3
Energy barriers and stabilization energies for proton transfer from site III to N1 of the model complex (Fig. 3) calculated with various basis sets

Level of computation[a]	Energy barrier	Stabilization energy	Total energy[b]
		kcal/mol	*hartrees*
I. STO-3G//STO-3G	10.3	21.8	−372.005557
II. 3-21G//3-21G	9.6	17.3	−374.594101
III. 4-31G//3-21G	11.8	20.2	−376.129353
IV. 6-31G//3-21G	12.6	20.0	−376.522837

[a] Notation is according to Ref. 21. For example, 6-31G//3-21G means single point calculation with the 6-31G basis set of a structure optimized with the 3-21G basis set.
[b] Values are for N3. . . H and N1. . . H distances of 1.0Å.

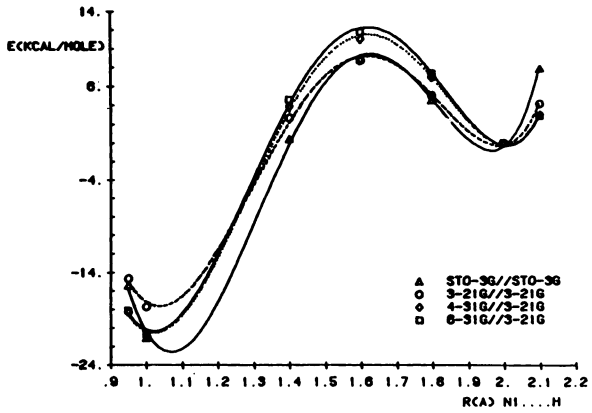

Fig. 4. Potential energy curves for proton transfer calculated for the model system shown in Fig. 3 with various basis sets: △, STO-3G//STO-3G; ○, 3-21G//3-21G; ◇, 4-31G//3-21G; □, 6-31G//3-21G. Notation is as in Ref. 22 and as defined in Table 3.

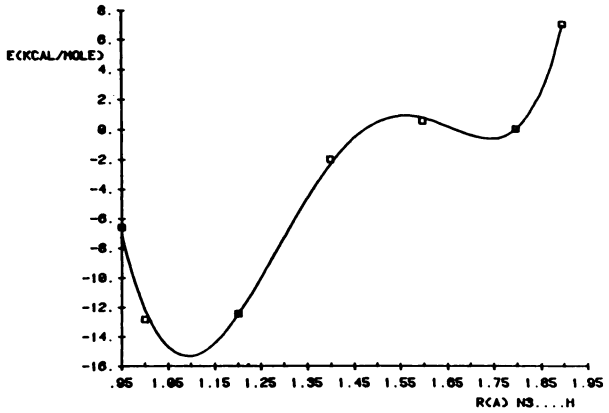

Fig. 5. Potential energy curve for proton transfer from N3 to site II, calculated with the STO-3G basis set for HA with neutral side chain and protonated N1 site. The energies (*E*) are calculated relative to the final point at which the proton is on site II and HA is in the N1-H tautomeric form. The energy of this state is 5.7 kcal/mol below the reference in Fig. 2.

Proton transfer from N3 to site II. A preliminary scan, with an all valence-electron semiempirical method, of the potential energy surface for the movement of protons from site III to N1 and from N3 to site II (results not shown) indicated that the movement will be sequential rather than concerted. This conclusion is also supported by results in Table 1 which show that the complex with the protonated imidazolium has the lowest energy and is bracketed by high energy barriers for proton transfer to either site II or site III (see also Figs. 2 and 5). We therefore report here the results of calculations of the transfer of the proton from N3 to site II only after the completion of the transfer from site III to N1. The potential energy curve for the movement of the proton from the N3 nitrogen of the protonated imidazolium (Fig. 5) is calculated for the optimized structures with the constraints described under Computational Details. The energy barrier for this process, calculated from the protonated imidazole (i.e., both N1 and N3 bear hydrogens) is 16.2 kcal/mol and the stabilization energy is negative (−14.8 kcal; see line VII of Table 1). However, because site II participates in the proton transfer as the proton acceptor, the molecular nature and the proton affinity of this site as well as the receptor environment will affect the feasibility of the proton release processes from N3; it may also change the energetics of the proton transfer from site III to N1.

To estimate such a possible influence of the environment on the proton transfer process to N1 of the histamine molecule anchored at the receptor site, we compared the potential surfaces obtained with ammonia as a proton acceptor at site II (Fig. 1) with those obtained in the absence of any proton acceptor site, and with a negatively charged hydroxyl group (OH^-) placed at that site. The results (Table 1) show that the presence of a proton acceptor near N3 has a profound effect both on the barrier and on the driving force to proton transfer from ammonium to the N1 nitrogen (i.e., from site III to N1). Thus, when the proton acceptor (NH_3) is absent from site II, we obtain the highest barrier and the lowest value of the driving force for the proton movement to N1 (18.9 and 9.1 kcal/mol, respectively; line I in Table 1). This might correspond to a situation before HA monocation is fully recognized and anchored at the receptor. In this situation, neutralization of the side chain lowers the barrier only by 3.5 kcal/mol and increases the driving force by 3 kcal/mol (lines I and II of Table 1). In contrast, replacing site II in Fig. 1 by a negatively charged group, OH^-, causes the value of the energy barrier to drop from 15.3 kcal/mol to 5.5 kcal/mol for histamine monocation with the protonated side chain (see Fig. 6 and line VI of Table 1). The driving force for the proton transfer to N1 increases more than 2-fold (15.8 versus 36.3 kcal/mol) as a consequence of the presence of the OH^- near N3. As before, neutralization of the side chain contributes to the further lowering of the barrier to 3.9 kcal/mol and adds another 2.9 kcal/mol to the stabilization energy (line VII of Table 1).

Thus, the calculations show that the presence of a proton acceptor at site II consistently diminishes the barrier and increases the driving force for proton movement from Site III toward N1; a negative site has a much larger effect on both parameters in spite of the considerable distance between the two receptor sites in the model. This indicates that the nature of the sites in the recognition pocket will affect the energy of the proton transfer process and is likely to be of great importance in the discrimination of agonists, partial agonists and antagonists at the H_2-receptor of HA. Using molecules with known agonist, antagonist, or partial agonist properties, it

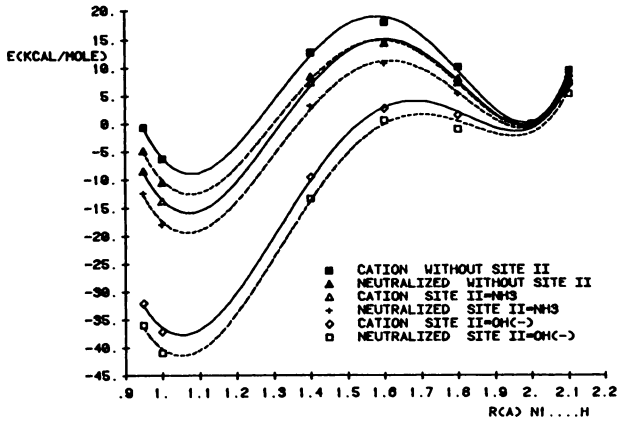

Fig. 6. Potential energy curves for proton transfer calculated with the STO-3G basis set with different groups at site II: ■, HA N3-H monocation, site II: none; ▲, neutralized HA monocation, site II: none; △, HA N3-H monocation, site II: NH_3; +, neutralized N3-H histamine monocation, site II: NH_3; ◇, HA N3-H monocation, site II: OH^-; □, neutralized histamine N3-H monocation, site II: OH^-.

should be possible to identify the most likely amino acid residues that can serve as proton donors and acceptors at sites III and II.

Conclusions

Results of calculations presented above show that the proton transfer postulated for the activation process of the HA H_2-receptor is energetically feasible. Such a proton transfer is facilitated by the neutralization of the ethylamine side chain of the HA monocation. The barrier and the driving force to the movement of the proton toward the N1 nitrogen are significantly reduced when various proton acceptors are placed near the N3 side. This strongly suggests that the environment can be a crucial factor in the triggering and facilitation of the proton relay mechanism at the H_2-HA receptor. Similar effects of the presence of ions on the proton transfer in small systems have recently been reported by Scheiner *et al.* (20).

The relatively high barrier to proton transfer from the protonated imidazole ring to the ammonia molecule at site II (which serves in our studies as a moderate proton acceptor) suggests that, if the charge relay is completed by the removal of the proton from N3, then site II must be a stronger proton acceptor and the environment must be conducive to such a process. Under these circumstances, the entire proton relay mechanism may change from sequential to concerted. As a consequence, the proton movement from the proton donor (site III) to the N1 nitrogen, will become the major component of the activation process. In the case of partial agonists (9), or some antagonists (12, 13), the availability of a proton-accepting region like the N1 of HA that is able to interact with a proton donating receptor site could be reduced, e.g., through formation of an intramolecular hydrogen bond with the side chain, eliminating a crucial component of the activation mechanism. The proposed model must therefore be refined and tested with the use of molecules *known* to act as agonists, partial agonists, and antagonists on the HA H_2-receptor, in order to produce a realistic scale of energies that would be predictive for the activity of other, untested compounds. The ability to explain the pharmacological activity of some partial agonists (9) and some antagonists (2, 12, 13) on this basis is currently being explored.

Acknowledgments

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Appendix

Atomic coordinates (in Å) for the optimized model shown in Fig. 1

Group	Atom name	X	Y	Z
Site I	O_1	−5.060470	−2.092243	0.852171
	H_{O1}	−6.017375	−1.854175	0.772351
Site II	N^A	2.521557	0.0	7.500794
	H_{NA1}	2.037055	0.0	8.411652
	H_{NA2}	3.153187	−0.814302	7.549378
	H_{NA3}	3.153187	0.814302	7.549378
Site III	N^D	0.0	0.0	0.0
	H_{ND1}	−0.007788	0.0	1.075447
	H_{ND2}	−0.976570	0.0	−0.358227
	H_{ND3}	0.488285	0.845735	−0.358227
	H_{ND4}	0.488285	−0.845735	−0.358227
HA cation	N_1	−0.106198	0.0	3.073025
	C_2	1.063941	0.0	3.714843
	H_2	2.040236	0.0	3.239420
	N_3	0.927777	0.0	5.080974
	H_3	1.608773	0.0	5.813261
	C_4	−0.429072	0.0	5.324896
	H_4	−0.825222	0.0	6.331015
	C_5	−1.056340	0.0	4.125861
	C_6	−2.580599	0.0	4.009424
	H_{6A}	−3.040348	−0.332083	4.939087
	H_{6B}	−2.948820	1.004038	3.788552
	C_7	−2.979419	−0.938651	2.850195
	H_{7A}	−2.847477	−1.994406	3.096923
	H_{7B}	−2.423687	−0.695430	1.941350
	N_8	−4.473019	−0.772708	2.501119
	H_{N8A}	−4.752072	−1.399519	1.717829
	H_{N8B}	−5.082694	−0.994268	3.315426
	H_{N8C}	−4.681606	0.205195	2.210785

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