Novel Stable Configurations and Tautomers of the Neutral and Deprotonated Hydroxamic Acids Predicted from High-Level ab Initio Calculations

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Hydroxamic acids, best known as iron chelators, have recently been widely used as a key functional group of potential therapeutics targeting at zinc-bound matrix metalloproteinases involved in cancers. To investigate the optimal structural variations of hydroxamic acids that confer the maximal selectivity for zinc over iron for rational design of cancer drugs, we have first performed calculations of hydroxamic acids in the absence of metal ions employing density functional, Møller−Plesset, and coupled cluster theories. Herein we report the high-level ab initio calculations of hydroxamic acids that offer new insights into the intricate structures of acetohydroxamic acid. The results suggest that in the gas phase acetohydroxamic acid exists in the *E*- and *Z*-keto forms and the *Z*-iminol form that are in equilibrium, whereas the deprotonated acetohydroxamic acid exists in the nitrogen-deprotonated *Z*-keto form and the *C*-hydroxy oxygen-deprotonated *Z*-iminol form that are in resonance. Substitution of the nitrogen proton of acetohydroxamic acid by a methyl group does not change the structures and relative stability of the neutral and deprotonated acetohydroxamic acid in different configurations and tautomers.

Introduction

Hydroxamic acids, best known as iron chelators,[1] have recently been widely used as a key functional group of potential therapeutics targeting at zinc-bound matrix metalloproteinases involved in cancers.[2−17] In our opinion, caution should be used when hydroxamic acids are used to design specific inhibitors of zinc proteins, since hydroxamic acids have high affinity for iron which is in fact the most abundant transition metal ion in human.[18] Accordingly we have performed a series of high-level ab initio calculations of hydroxamic acids in the absence of metal ions employing DFT, Møller−Plesset, and coupled cluster theories.

The present study is focused on theoretical predictions in the gas phase on the relative acidities and stable configurations and tautomers of the neutral and deprotonated acetohydroxamic and *N*-methylacetohydroxamic acids that can serve as model hydroxamic acids used in cancer drug design. It has long been assumed that acetohydroxamic acid can exist in either keto (**1** and **2**) or iminol (**3**−**7**) form that each can be present in either the *E* or *Z* configuration about the C−N bond (Figure 1).[19] Several theoretical calculations have been reported for hydroxamic acids.[20−25] The calculations with the MP2 theory suggest **1** (*E*-keto) to be the most stable structure in the gas phase,[22,23] while the X-ray crystallographic analysis of acetohydroxamic acid revealed the stable structure to be in the *Z*-keto form in the solid state.[26] The predicted most stable *E*-keto form in the gas phase seemed to be contrary to the fact that an intramolecular hydrogen bond in the *Z* form is disabled in the *E* form (Figure 1). No ab initio calculations of *N*-methylacetohydroxamic acid with consideration of electron correlation effect have been reported so far, and yet this molecule has been widely used as a functional group in rational drug design. These considerations prompted us to investigate the stable structures of acetohydroxamic and *N*-methylacetohydroxamic acids and the relative acidities and stable deprotonation sites of the two acids with higher level ab initio calculations. It has been reported that electron correlation effect is important in the theoretical studies of hydroxamic acids.[25] Density functional, many-body perturbation, and coupled-cluster theories with large basis sets including diffuse and polarization functions have thus been used in the present study in an attempt to resolve the conflict and to investigate which level of ab initio methods is computationally affordable and adequate to study hydroxamic acids.

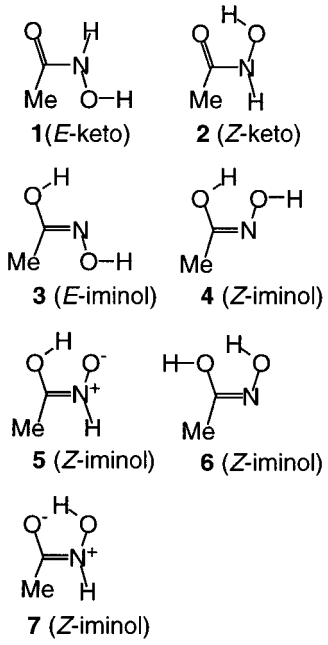

Figure 1. Different tautomers and configurations of acetohydroxamic acid.

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TABLE 1: Relative Energies (kcal/mol) of the Different Structures of Acetohydroxamic Acid versus Calculation Methods

method	**1** (*E*-keto)	**2** (*Z*-keto)	**3** (*E*-iminol)	**4** (*Z*-iminol)	**5** (*Z*-iminol)	**6** (*Z*-iminol)
B3LYP/6-311+G(2d,2p)// B3LYP/6-311+G(2d,2p)	1.9	0	6.9	2.9	11.7	11.2
CCSD(T)/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.8	1.0	2.6	0	13.7	2.4
MP2/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.5	0.0	4.9	0.7	14.6	9.9
MP3/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.8	1.0	3.9	0	17.5	9.0
MP4D/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.7	1.0	3.9	0	17.0	8.9
MP4DQ/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0	0.5	3.9	0	17.4	9.0

TABLE 2: Relative Energies (kcal/mol) of the Different Structures of the Deprotonated Acetohydroxamic Acid versus Calculation Methods

method	**1A1** (*E*-keto)	**1A2** (*Z*-keto)	**2A1** (*Z*-keto)	**2A2** (*Z*-keto)	**3A1** (*E*-iminol)
B3LYP/6-311+G(2d,2p)// B3LYP/6-311+G(2d,2p)	11.6	8.1	0	13.4	26.7
CCSD(T)/6-311+G(d,p)// B3LYP/6-311+G(d,p)	11.9	12.3	0	18.7	27.7
MP2/6-311+G(d,p)// B3LYP/6-311+G(d,p)	13.1	12.8	0	18.7	28.2
MP3/6-311+G(d,p)// B3LYP/6-311+G(d,p)	12.5	12.9	0	19.6	28.3
MP4D/6-311+G(d,p)// B3LYP/6-311+G(d,p)	12.5	13.1	0	19.5	27.7
MP4DQ/6-311+G(d,p)// B3LYP/6-311+G(d,p)	12.3	12.6	0	19.2	28.0

Methods

The ab initio calculations were carried out by using the Gaussian 94 program[27] running on a SGI Origin 2000 (8 × 195 MHz, 2.0 GB memory, and 40 GB disk) and four Origin 200s (8 × 180 MHz, 1.2 GB memory, and 16 GB disk). The structures of hydroxamic acids were first generated with the Quanta program and optimized by energy minimization with the CHARMm molecular mechanics force field.[28] Further geometry optimizations and harmonic frequencies used to preclude the low-energy transition-state geometries were computed by using Becke's three-parameter formulation (B3LYP) density functional method[29,30] with the 6-311+G(d,p) and 6-311+G(2d,2p) basis sets, respectively.[31] The relative energies of different structures of hydroxamic acids were obtained from the B3LYP-optimized geometries with the methods of B3LYP,[32,29] CCSD(T),[33] and Møller−Plesset perturbation (MP2,[34−39] MP3,[40,41] MP4D,[42] and MP4DQ[42]). The triplet-state energies of all molecules in the present study were also calculated, but they are not reported since such energies were found to be higher than the singlet-state energies.

Results and Discussion

Acetohydroxamic Acid. The relative energies of different structures of the neutral and deprotonated acetohydroxamic acids (Figures 1 and 2) and the corresponding bond lengths, angles, and torsions are listed in Tables 1−4. Structure **7** (*Z*-iminol) converged to **2** (*Z*-keto) after the B3LYP/6-311+G(2d,2p) optimization. The calculations with the B3LYP/6-311+G(2d,-2p) method suggest that **2** (*Z*-keto, 0 kcal/mol) is the most stable structure followed by **1** (*E*-keto, 1.9 kcal/mol), **4** (*Z*-iminol, 2.9 kcal/mol), **3** (*E*-iminol, 6.9 kcal/mol), and the other two most energetic *Z*-iminol forms (**6** and **5**, 11.2 and 11.7 kcal/mol, respectively) (Table 1). This suggests that acetohydroxamic acid exists in **1** (*E*-keto) and **2** (*Z*-keto) and **4** (*Z*-iminol) forms that

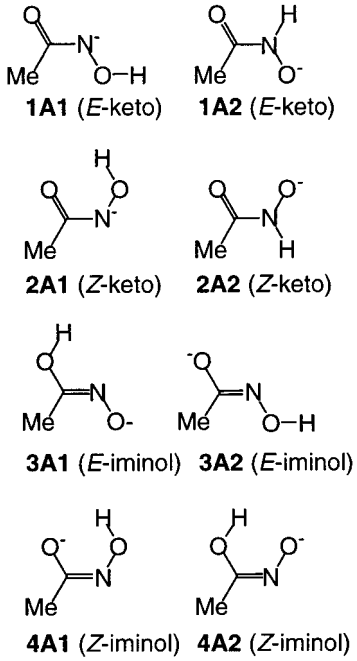

Figure 2. Different tautomers and configurations of the deprotonated acetohydroxamic acid.

are in equilibrium in the gas phase, according to the chemical accuracy (ca. 2 kcal/mol)[43] and the fact that energy difference of 3.0 kcal/mol implies that 99% of a population is composed of one conformation at equilibrium at room-temperature according to $\Delta G = -RT \ln K$. This prediction is consistent with the calculations employing the CCSD(T) method that is almost as accurate as the full configuration interaction if the nondynamical correlation effects are not important.[44] Interestingly, the CCSD(T) method reduces the energy differences of the three stable structures and change the rank order of stability showing

TABLE 3: Bond Lengths (Å), Angles (deg of arc), and Torsions (deg of arc) of the Different Structures of Acetohydroxamic Acid Optimized with the B3LYP/6-311+G(2d,2p) Method

	1 (*E*-keto)	**2** (*Z*-keto)	**3** (*E*-iminol)	**4** (*Z*-iminol)	**5** (*Z*-iminol)	**6** (*Z*-iminol)
CO	1.225	1.226	1.357	1.348	1.326	1.373
CC	1.506	1.508	1.492	1.488	1.480	1.491
CN	1.363	1.364	1.273	1.278	1.301	1.271
NH	1.008	1.009			1.015	
NO	1.400	1.399	1.420	1.432	1.314	1.396
OH	0.978	0.979	0.967	0.960	0.993	0.969
OCN	119.7	119.7	117.7	124.4	114.9	120.4
OCC	124.2	124.3	114.9	115.0	120.0	118.6
CNO	115.9	116.5	111.0	109.2	120.6	116.0
HNO	111.0	111.0			118.9	
HNC	121.1	121.1			120.5	
NOH	101.3	111.0	102.2	102.8		−108.4
HNCC	156.7	32.8			−0.3	
OCNO	−157.5	−10.5	−180.0	0	0	−0.3
CNOH	−119.3	4.5	180.0	179.7		0
OCCH	−4.5	−178.3	0	−180.0	180.0	−180.0

TABLE 4: Bond Lengths (Å), Angles (deg of arc), and Torsions (deg of arc) of the Different Structures of the Deprotonated Acetohydroxamic Acid Optimized with the B3LYP/6-311+G(2d,2p) Method

	1A1 (*E*-keto)	**1A2** (*E*-keto)	**2A1** (*Z*-keto)	**2A2** (*Z*-keto)	**3A1** (*E*-iminol)
CO	1.264	1.263	1.278	1.247	1.410
CC	1.537	1.515	1.518	1.532	1.484
CN	1.322	1.330	1.315	1.339	1.279
NH		1.016		1.016	
NO	1.505	1.357	1.446	1.336	1.335
OH	0.958		0.982		0.970
OCN	122.1	123.4	126.1	126.8	117.5
OCC	118.1	122.1	119.4	119.2	114.8
CNO	109.4	127.3	108.9	128.6	120.3
HNO		117.8			
HNC			115.3		
NOH	98.4		101.4		
HNCC		180.0		0	
OCNO	180.0	180.0	0	0	
CNOH	180.0		0		
OCCH	0	0.6	180.0	180.0	−180.0

the *Z*-iminol form to be most stable. The results of the calculations using the higher order Møller−Plesset methods (MP3 and MP4) are consistent with those using the CCSD(T) methods, whereas the result using the second-order Møller−Plesset method (MP2) agrees with that using the B3LYP method. Nonetheless, all the high-level ab initio calculations suggest the presence of the *Z*-keto and *Z*-iminol forms in the gas phase that were precluded by the reported ab initio calculations.[23,22]

For the deprotonated acetohydroxamic acid, **3A2** (*E*-iminol), **4A1** (*Z*-iminol), and **4A2** (*Z*-iminol) converged to **1A1** (*E*-keto), **2A1** (*Z*-keto), and **2A1** (*Z*-keto), respectively, after the B3LYP/6-311+G(2d,2p) optimization. All our high-level ab initio calculations suggest that **2A1** (*Z*-keto) is most stable and the rest are at least 8.1 kcal/mol more energetic (Table 2), which is consistent with the reported ab initio calculations.[22,23] As depicted in Figure 3, the CO bond (1.278 Å) in the structure converged from **2A1** (*Z*-keto) and **4A1** (*Z*-iminol) is longer than the CO double bond in **2** (*Z*-keto) (1.225 Å) and shorter than the CO single bond in **4** (*Z*-iminol) (1.348 Å); conversely, the CN bond (1.315 Å) in the structure converged from **2A1** (*Z*-keto) and **4A1** (*Z*-iminol) is shorter than the CN single bond in **2** (*Z*-keto) (1.363 Å) and longer than the CN double bond in **4** (*Z*-iminol) (1.278 Å). In addition, the largest difference in charge (0.3827) between **2** (*Z*-keto) and the structure converged from **2A1** (*Z*-keto) and **4A1** (*Z*-iminol) is at the nitrogen atom of **2** (*Z*-keto), implying that deprotonation occurs at the nitrogen atom of **2** (*Z*-keto), while the largest difference in charge (0.3446) between **4** (*Z*-iminol) and the structure converged from **2A1** (*Z*-keto) and **4A1** (*Z*-iminol) is at the oxygen atom of **4** (*Z*-iminol), implying that deprotonation occurs at the *C*-hydroxy oxygen atom of **4** (*Z*-iminol). These results suggest that **2A1** (*Z*-keto) is in resonance with **4A1** (*Z*-iminol). In contrast to the reported study in which the presence of the *C*-hydroxy oxygen-deprotonated *Z*-iminol form (**4A1**) was overlooked,[23] these results suggest that the deprotonated acetohydroxamic acid exists in the nitrogen-deprotonated *Z*-keto form (**2A1**) and the *C*-hydroxy oxygen-deprotonated *Z*-iminol form (**4A1**) that are in resonance in the gas phase, which is akin to the report in reference.[22]

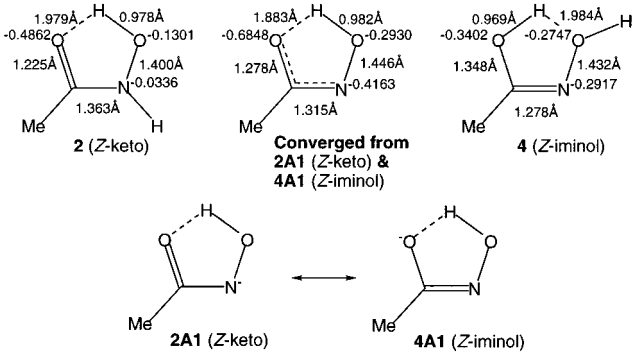

Figure 3. Resonance structures of the most stable deprotonated acetohydroxamic acid implied by the bond lengths and charges of the deprotonated and the corresponding neutral acetohydroxamic acids (the charges were derived from the CCSD(T) calculations).

***N*-Methylacetohydroxamic Acid.** The relative energies of the different structures of the neutral and deprotonated *N*-methylacetohydroxamic acids (Figure 4) and the corresponding bond lengths, angles, and torsions are listed in Tables 5−7. Structure **9** (*E*-iminol) converged to **7** (*E*-keto) after the B3LYP/6-311+G(2d,2p) optimization. The B3LYP calculations suggest that **8** (*Z*-keto, 0 kcal/mol) is the most stable structure followed by **10** (*Z*-iminol, 1.5 kcal/mol) and **7** (*E*-keto, 1.7 kcal/mol) (Table 5). This suggests that the *N*-methyl acetohydroxamic acid also exists in **7** (*Z*-keto), **8** (*E*-keto), and **10** (*Z*-iminol) that are in equilibrium in the gas phase like acetohydroxamic acid. This result is also consistent with the CCSD(T) calculations. Interestingly, the CCSD(T) calculations increase the energy difference between the keto and iminol forms. Again, the results of the higher order Møller−Plesset calculations (MP3 and MP4) are consistent with those of the CCSD(T) calculations, whereas the

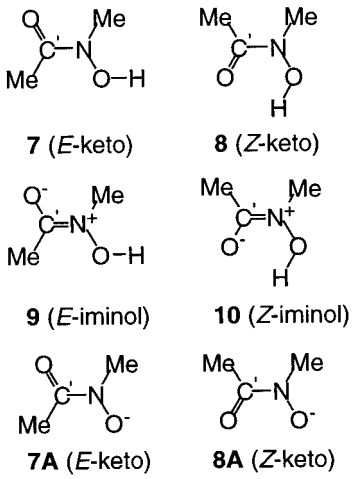

Figure 4. Different tautomers and configurations of the neutral and deprotonated *N*-methylacetohydroxamic acids.

TABLE 5: Relative Energies (kcal/mol) of the Different Structures of *N*-Methylacetohydroxamic Acid versus Calculation Methods

method	**7** (*E*-keto)	**8** (*Z*-keto)	**10** (*Z*-minol)
B3LYP/6-311+G(2d,2p)// B3LYP/6-311+G(2d,2p)	1.7	0	1.5
CCSD(T)/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0	0	2.2
MP2/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.6	0	2.2
MP3/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0	0.5	2.5
MP4D/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0	0.4	2.5
MP4DQ/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0	0.7	2.7

TABLE 6: Relative Energies (kcal/mol) of the Different Structures of the Deprotonated *N*-Methylacetohydroxamic Acid versus Calculation Methods

method	**7A** (*E*-keto)	**8A** (*Z*-keto)
B3LYP/6-311+G(2d,2p)// B3LYP/6-311+G(2d,2p)	0.0	10.4
CCSD(T)/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.0	9.8
MP2/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.0	9.4
MP3/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.0	11.2
MP4D/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.0	10.3
MP4DQ/6-311+G(d,p)// B3LYP/6-311+G(d,p)	0.0	10.9

result using the second-order Møller−Plesset method (MP2) agrees with that of the B3LYP method. For the deprotonated *N*-methylacetohydroxamic acid (Table 6), all the high-level ab initio calculations suggest that **7A** (*E*-keto) is at least 9.4 kcal/mol more stable than **8A** (*Z*-keto). These results suggest that substitution of the NH proton by a methyl group does not alter the structures and relative stabilities of acetohydroxamic acids in different configurations and tautomeric forms.

Intramolecular Hydrogen Bond. As apparent from Table 1, the highest level ab initio calculation in the present study employing the CCSD(T) method suggests that the energy differences between the *Z* and *E* configurations for the keto form of acetohydroxamic and *N*-methylacetohydroxamic acids are less than the hydrogen bond energy that is in the range of 2−5 kcal/mol.[45] This seems to be inconsistent with the fact that an intramolecular hydrogen bond in the *Z* configuration is disabled in the *E* configuration. To resolve this conflict, we examined the structures of **2** (*Z*-keto) and **8** (*Z*-keto) optimized with the B3LYP/6-311+G(2d,2p) method. Surprisingly, the angles of HOC in **2** and **8** (83° and 85° of arc, respectively) are in fact less than the cutoff angle (90° of arc) to form a hydrogen bond.[45] These results imply that the intramolecular hydrogen bonds in both **2** (*Z*-keto) and **8** (*Z*-keto) are disabled, thus explaining why the *E* configuration is nearly as stable as the *Z* configuration and why the relative stability of the *Z* and *E* configurations is environment-dependent.[22,25,23]

TABLE 7: Bond Lengths (Å), Angles (deg of arc), and Torsions (deg of arc) of the Different Structures of the Neutral and Deprotonated *N*-Methylacetohydroxamic Acids Optimized with the B3LYP/6-311+G(2d,2p) Method

	7 (*E*-keto)	**8** (*Z*-keto)	**10** (*Z*-minol)	**7A** (*E*-keto)	**8A** (*Z*-keto)
C′O	1.218	1.233	1.326	1.262	1.248
C′C	1.511	1.511	1.484	1.515	1.541
C′N	1.385	1.355	1.307	1.336	1.344
NC	1.453	1.441	1.455	1.443	1.449
NO	1.415	1.403	1.325	1.359	1.346
OH	0.964	0.981	1.001		
OC′N	120.3	119.0	114.2	124.7	124.6
OC′C	123.1	122.8	117.3	121.3	117.9
CNO	115.7	114.6	115.7	123.5	123.91
NOH	104.9	100.8			
CNC′	121.2	129.9	127.2	121.0	124.1
CNC′C	161.9	19.4	0	−180.0	0
OC′NO	−162.7	−6.0	0	−180.0	0
C′NOH	−114.6	4.0			
OC′CH	−4.7	−12.0	180.0	0	0

Electron Correlation. For acetohydroxamic acid, as apparent from Table 1, the presence of **4** (*Z*-iminol) predicted by the CCSD(T) method was precluded in the gas phase by the reported low-level ab initio calculations that did not take into account electron correlation.[24] Although the B3LYP and MP2 calculations change the rank order of stability of **1**−**4** predicted by CCSD(T) method, the energy differences of these structures are less than 3 kcal/mol and thus insignificant considering the chemical accuracy (ca. 2 kcal/mol).[43] These results suggest also that the HF method is not adequate to study the neutral hydroxamic acids and the B3LYP method or higher level theories should be used to count for electron correlation required in the study of the neutral acetohydroxamic acids.

Conclusions

On the basis of the calculations employing the density functional, Møller−Plesset, and coupled cluster theories, in the gas phase acetohydroxamic acid exists in the *E*- and *Z*-keto forms and the *Z*-iminol form that are in equilibrium, whereas the deprotonated acetohydroxamic acid exists in the nitrogen-deprotonated *Z*-keto form and the *C*-hydroxy oxygen-deprotonated *Z*-iminol form that are in resonance. Substitution of the nitrogen proton of acetohydroxamic acid by a methyl group does not significantly alter the structures and relative stability of the neutral and deprotonated acetohydroxamic acid. The intramolecular hydrogen bond is disabled in the *Z*-keto form of both acetohydroxamic and *N*-methyl acetohydroxamic acids in the gas phase.

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References and Notes

(1) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563−1579.
(2) Bode, W.; Reinemer, P.; Huber, R.; Kleine, T.; Schnierer, S.; Tschesche, H. *EMBO J.* **1994**, *13*, 1263−9.
(3) Brandstetter, H.; Engh, R. A.; Von Roedern, E. G.; Moroder, L.; Huber, R.; Bode, W.; Grams, F. *Protein. Sci.* **1998**, *7*, 1303−9.
(4) DiMartino, M.; Wolff, C.; High, W.; Stroup, G.; Hoffman, S.; Laydon, J.; Lee, J. C.; Bertolini, D.; Galloway, W. A.; Crimmin, M. J.; Davis, M.; Davies, S. *Inflamm. Res.* **1997**, *46*, 211−5.
(5) Ferry, G.; Boutin, J. A.; Hennig, P.; Genton, A.; Desmet, C.; Fauchere, J. L.; Atassi, G.; Tucker, G. C. *Eur. J. Pharmacol.* **1998**, *351*, 225−233.
(6) Groneberg, R. D.; Burns, C. J.; Morrissette, M. M.; Ullrich, J. W.; Morris, R. L.; Darnbrough, S.; Djuric, S. W.; Condon, S. M.; McGeehan, G. M.; Labaudiniere, R.; Neuenschwander, K.; Scotese, A. C.; Kline, J. A. *J. Med. Chem.* **1999**, *42*, 541−4.
(7) Holleran, W. M.; Galardy, R. E.; Gao, W. N.; Levy, D.; Tang, P. C.; Elias, P. M. *Arch. Dermatol. Res.* **1997**, *289*, 138−44.
(8) Jacobson, I. C.; Reddy, P. G.; Wasserman, Z. R.; Hardman, K. D.; Covington, M. B.; Arner, E. C.; Copeland, R. A.; Decicco, C. P.; Magolda, R. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 837−42.
(9) Maskos, K.; Fernandez-Catalan, C.; Huber, R.; Bourenkov, G. P.; Bartunik, H.; Ellestad, G. A.; Reddy, P.; Wolfson, M. F.; Rauch, C. T.; Castner, B. J.; Davis, R.; Clarke, H. R.; Petersen, M.; Fitzner, J. N.; Cerretti, D. P.; March, C. J.; Paxton, R. J.; Black, R. A.; Bode, W. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3408−12.
(10) Nixon, J. S.; Bottomley, K. M.; Broadhurst, M. J.; Brown, P. A.; Johnson, W. H.; Lawton, G.; Marley, J.; Sedgwick, A. D.; Wilkinson, S. E. *Int. J. Tissue React.* **1991**, *13*, 237−41.
(11) Odake, S.; Morita, Y.; Morikawa, T.; Yoshida, N.; Hori, H.; Nagai, Y. *Biochem. Biophys. Res. Commun.* **1994**, *199*, 1442−6.
(12) Pikul, S.; McDow Dunham, K. L.; Almstead, N. G.; De, B.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider, C. E.; Taiwo, Y. O.; Chen, L.; Dunaway, C. M.; Gu, F.; Mieling, G. E. *J. Med. Chem.* **1999**, *42*, 87−94.
(13) Preece, G.; Murphy, G.; Ager, A. *J. Biol. Chem.* **1996**, *271*, 11634−11640.
(14) Steinman, D. H.; Curtin, M. L.; Garland, R. B.; Davidsen, S. K.; Heyman, H. R.; Holms, J. H.; Albert, D. H.; Magoc, T. J.; Nagy, I. B.; Marcotte, P. A.; Li, J.; Morgan, D. W.; Hutchins, C.; Summers, J. B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2087−92.
(15) Steinmann-Niggli, K.; Lukes, M.; Marti, H. P. *J. Am. Soc. Nephrol.* **1997**, *8*, 395−405.
(16) Steinmeyer, J.; Daufeldt, S.; Kalbhen, D. A. *Pharmacology* **1997**, *55*, 95−108.
(17) Vandyk, D. E.; Marchand, P.; Bruckner, R. C.; Fox, J. W.; Jaffee, B. D.; Gunyuzlu, P. L.; Davis, G. L.; Nurnberg, S.; Covington, M.; Decicco, C. P.; Trzaskos, J. M.; Magolda, R. L.; Copeland, R. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1219−1224.
(18) Christianson, D. W. *Adv. Protein Chem.* **1991**, *42*, 281−355.
(19) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376−384.
(20) Brown, D. A.; Coogan, R. A.; Fitzpatrick, N. J.; Glass, W. K.; Abukshima, D. E.; Shiels, L.; Ahlgren, M.; Smolander, K.; Pakkanen, T. T.; Pakkanen, T. A.; Perakyla, M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2673−2679.
(21) Yamin, L. J.; Ponce, C. A.; Estrada, M. R.; Vert, F. T. *J. Mol. Struct., (THEOCHEM)* **1996**, *360*, 109−117.
(22) Ventura, O. N.; Rama, J. B.; Turi, L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 5754−5761.
(23) Bagno, A.; Comuzzi, C.; Scorrano, G. *J. Am. Chem. Soc.* **1994**, *116*, 916−924.
(24) Turi, L.; Dannenberg, J. J.; Rama, J.; Ventura, O. N. *J. Phys. Chem.* **1992**, *96*, 3709−3712.
(25) Wu, D.-H.; Ho, J.-J. *J. Phys. Chem.* **1998**, *102*, 3582−3586.
(26) Bracher, B. H.; Small, R. W. H. *Acta Crystallogr.* **1970**, *26B*, 1705.
(27) Frisch, M. J.; Trucks, G. W.; H. B., S.; Gill, P. M. W.; Hohnson, B. G.; Robb, M. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; R. L., M.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzales, C.; Pople, J. A. *GAUSSIAN 94*, revision D.4; Gaussian Inc.: Pittsburgh, PA, 1995.
(28) QUANTA/CHARMm, 1997 ed.; Molecular Simulations Inc.: San Diego, CA, 1997.
(29) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(30) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 1988.
(31) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(32) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(33) Raghavachari, K.; Trucks, G. H.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479.
(34) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.
(35) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett* **1988**, *153*, 503.
(36) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 275.
(37) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 281.
(38) Head-Gordon, M.; Head-Gordon, T. *Chem. Phys. Lett.* **1994**, *220*, 122.
(39) Saebo, S.; Almlof, J. *Chem. Phys. Lett.* **1989**, *154*, 83.
(40) Pople, J. A.; Seeger, R.; Krishnan, R. *Int. J. Quantum Chem. Symp.* **1977**, *11*, 149.
(41) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem. Symp.* **1976**, *10*, 1.
(42) Krishnan, R.; Pople, J. A. *Int. J. Quantum Chem.* **1978**, *14*, 91.
(43) Remko, M.; Liedl, K. R.; Rode, B. M. *J. Phys. Chem.* **1998**, *102*, 771−777.
(44) Lee, T. J.; Taylor, P. R. *Int. J. Quantum Chem. Symp.* **1989**, *23*, 199.
(45) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, Germany, 1991.