

Ab Initio Calculation of Torsion and Inversion Barriers of the Amino Group in Aminopyrimidines

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Calculations of the barriers to internal rotation and inversion of the amino group in substituted pyrimidines have been performed. Torsion and inversion barriers were determined by several ab initio methods: HF, HF/MP2, MP4, CISD, QCISD, QCISD(T), CCSD, and CCSD(T). DFT method also employed. Dependencies of the calculated barrier heights on the basis set and the electron correlation level and on the substitution position of the nitrogen atom in the ring were studied. We have determined that for certain molecules relatively low level calculations may eventually provide adequate results, but in general, higher level calculations are necessary.

Introduction

Quantum chemical (QC) calculations of rotational barriers in substituted aromatic molecules are interesting both theoretically and for applications to biochemistry and pharmaceutical drug design. Until now, it has not been clear what level of theory is needed to reproduce the barriers of internal rotations with acceptable accuracy for a broad range of molecules. This problem is made difficult by the fact that various phenomena (intermolecular charge transfer, dispersion, and lone pair electron delocalization) can influence the energetics of internal rotations in molecules, and an ideal quantum chemical method must take all of them into account in a balanced way. It seems that accurate calculation of phenomena such as charge transfer or dispersion requires high-level correlated QC methods like CCSD (coupled cluster singles and doubles). However, the vast majority of reported calculations of rotational barriers were performed by relatively simple techniques (HF, HF/MP2, and DFT) and/or using small basis sets not suited for correlated QC calculations. The accuracy of such data is questionable. On the other hand, high level studies have only been performed for relatively simple molecules.

There is a growing practical need for accurate estimations of internal rotation barriers for a broad range of organic molecules. The barriers are utilized in molecular mechanics and dynamics simulations, especially in drug design, when drug candidates possess many internal degrees of freedom. The correct representation of multidimensional energy landscapes of such molecules is required for successful simulation of protein–ligand interaction, flexible ligand docking, and so on. Such calculations are usually performed using universal force fields such as Amber and MMFF, but validation of the force field estimated barriers by more rigorous QC methods is highly desirable.

Rotation of functional groups in various substituted aromatics has been studied by a number of authors^{1–17} but at relatively

low levels of theory. In ref 1, the amino group rotation in aniline was studied theoretically (AM1, PM3, SAM1 methods; the HF/MP2 calculation level with the 6-311G** basis set; and a number of density functional methods with the 6-31G**...6-311++G(3df, pd) basis sets). Experimentally, rotation and inversion of the amino group in aniline were studied in refs 2–4. Study of the hydroxyl group in substituted phenols was carried out experimentally,^{5,6} and at the B3LYP level with the 6-31G** basis set,⁷ and at the QCISD(T)/6-31G*, MP2/6-31+G**, and MP2/6-31++G(2df,p) calculation levels.⁸ Barriers to nitro group rotation in benzene derivatives have been extensively investigated in refs 9 and 10 at the B3LYP/6-311G** level and in ref 11 at the HF/6-31G* and the MP2/6-31G* calculation levels. Rotation of the methyl group in a number of benzene derivatives was studied in refs 12–14; torsion barriers were calculated at the HF/6-31G,¹³ B3LYP/cc-pVDZ¹², and MP2/6-311G**¹⁴ levels; experimental data for some of the molecules was also obtained. In refs 15–17, torsion barriers of some benzene derivatives were obtained theoretically by various methods of calculation and experimentally. So, we can see that only the simplest methods of correlated calculations and relatively small basis sets have been employed for internal rotation barriers calculations in most published works and the systematic investigation of the influence of the theory level on the calculated barrier heights has not been conducted yet.

In the current work, we have studied the barriers to internal rotation (torsion) and inversion of the amino group in isomeric aminopyrimidines (Figure 1): 2-aminopyrimidine (2-AP), 4-aminopyrimidine (4-AP), and 5-aminopyrimidine (5-AP). The aminopyrimidine motif is widespread in drug compounds, and the aminopyrimidines represent the simplest model for study of amino group rotation in nuclear bases. Also, they are interesting objects for testing the performance of different QC techniques, because the various phenomena mentioned above affect their equilibrium geometries, internal rotation, and inversion barriers. Calculations of aniline as a carbocyclic analogue of aminopyrimidines and of 5-nitropyrimidine (5-NP) as another substituted pyrimidine have also been performed for comparison. To our knowledge, no reports of the internal

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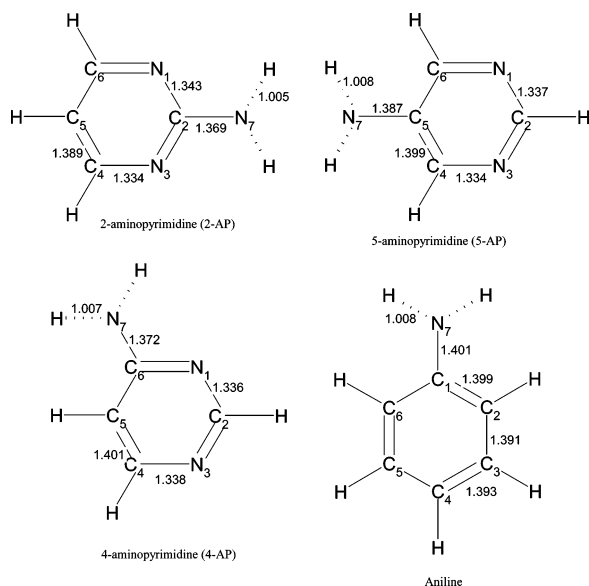


Figure 1. Structures of the studied aminopyrimidines and aniline with some bond lengths in Å (cc-pVTZ, HF/MP2 optimized geometries).

rotational barriers of the amino group of the pyrimidines investigated here have been presented either experimentally or theoretically.

In contrast to previous studies of rotation in aromatics, we employed a series of methods of different levels of sophistication, including Moller–Plesset perturbation methods of increasing orders (MP2, MP3, and MP4);¹⁸ configuration interaction (CI)¹⁹ with single and double excitations (CISD);^{20,21} quadratic CI with singles and doubles (QCISD)²² and with the perturbative triples correction QCISD(T);²² coupled cluster methods with singles and doubles CCSD²³ and with the perturbative triples correction CCSD(T).²⁴ Taking into account the growing popularity of DFT methods we also present some calculations of barriers heights using widespread B3LYP hybrid functional. Comparative results with these methods are presented below.

Theoretical Basis. All calculations were performed using the MOLPRO package.^{25–35} We used the two first basis sets in the family of Dunning correlation-consistent basis sets cc-pVXZ with X = 2 and 3 (cc-pVDZ and cc-VTZ).^{35–37} Coupled clusters calculations of aminopyrimidines in Dunning basis sets with X > 3 are currently almost impossible due to insufficient computational resources.

The heights of torsion and inversion barriers were calculated as the difference of the ground state and the saddle point energies. The geometry of stationary points (energy minima and saddle points for rotation and inversion) was determined by full geometry optimization at the HF/MP2 levels with cc-pVDZ or cc-pVTZ basis set (see Table 5) taking into account the symmetry group of the molecules (Table 1). The nature of the stationary points was proved by vibrational analysis (one imaginary frequency for saddle points, all real frequencies for true minima).

The HF/MP2 optimized geometries were used to calculate the respective energies by a series of QC methods: HF; the family of Moller–Plesset methods of increasing order (MP2, MP3, and MP4(SDTQ)); configuration interaction with singles and doubles (CISD); and a number of coupled clusters methods of different level (QCISD, CCSD, QCISD(T), and CCSD(T)). It is impossible to perform full CI calculations in our situation to find an exact correlation energy, but CCSD(T) recovers practically all of the correlation energy for a given basis set,³⁸ so the CCSD(T) results are used as a benchmark for other

TABLE 1: Structures of the Critical Points of the Studied Molecules

Molecule	2-AP	4-AP	5-AP	Aniline	5-NP
Minimum energy geometry					
Symmetry group	C _s	C ₁	C _s	C _s	C _{2v}
Rotation saddle point geometry					
Symmetry group	C _s	C _s (cis) C _s (trans)	C _s	C _s	C _{2v}
Inversion saddle point geometry					-
Symmetry group	C _{2v}	C _s	C _{2v}	C _{2v}	-

TABLE 2: Parameters of Geometry (Bond Length in Å, Angles in Degrees) for the Studied Molecules (cc-pVTZ, HF/MP2 Optimized)

	C _a –N7	C4–C5	N1–C2	N3–C4	N–H	C _a –N–H	H–N–H
2-AP	1.369	1.389	1.343	1.334	1.005	115.29	116.84
4-AP	1.372	1.401	1.336	1.338	1.007	117.02	115.15
5-AP	1.387	1.399	1.337	1.334	1.008	114.39	111.31
	C _a –N7	C1–C2	C2–C3	C3–C4	N–H	C _a –N–H	H–N–H
aniline	1.401	1.399	1.391	1.393	1.008	113.25	110.22

methods. Using small and medium size basis sets, a substantial basis set truncation error can be introduced, so extrapolation to the complete basis set was performed for the CCSD(T) results according to the approach proposed in refs 39 and 40. The HF and correlation energies, were extrapolated, according to expressions

$$E^{\text{HF}}(n) = E_{\infty}^{\text{HF}} + A^{\text{HF}} n^{-\alpha} \quad (1)$$

and

$$E^{\text{corr}}(n) = E_{\infty}^{\text{corr}} + A^{\text{corr}} n^{-\beta} \quad (2)$$

where $n = 2$ and 3 are for double and triple- ζ basis sets respectively, ∞ denotes the values for complete basis set limit, and α and β are assumed to be universal parameters. A^{HF} and A^{corr} are the constant for a given molecule. These constants, along with E_{∞}^{HF} and E_{∞}^{corr} can be found by solving the system of eqs 1 and 2 with $n = 2$ and 3 . The values of α and β were taken from refs 39 and 40.

In the case of the DFT method, we use B3LYP hybrid functional with cc-pVTZ basis set. The geometry optimization for these calculations was also performed in framework of DFT.

Symmetry group C_s of the ground state of the 2-AP, 5-AP, and aniline molecules implies the presence of a plane of symmetry which is perpendicular to the plane of the aromatic ring and contains the C_a–N bond. In general, this bond can be out of the ring plane, as well as the hydrogen atoms of the amino group. There are two planes of symmetry in the ground state of the 5-NP molecule (C_{2v}), one of which coincides with the plane of the aromatic ring and the other one of which is perpendicular to the ring.

TABLE 3: Calculated (cc-pVTZ, HF/MP2 Optimized Geometry) and Experimental Parameters of the Aniline (Bond Length in Å, Angles in Degrees)^a

	Geometry							
	C1–C2	C2–C3	C3–C4	C1–N	C2–H	C3–H	C4–H	N–H
exp.	1.4	1.39	1.39	1.39	1.07	1.08	1.07	1.04
calc.	1.399	1.391	1.393	1.401	1.083	1.082	1.081	1.008
	C2–C3–C4	C3–C4–C5	C2–C1–C6	C2–C1–N	C–N–H	H–N–H	C1–C2–C3	
	exp.	120.7	118	118	120	117	113	120.1
calc.	120.53	119.09	118.61	120.65	113.25	110.22	120.63	
Energy (in kcal/mol)								
calculation (CCSD(T) extrapolation to CBS)								
this work								
	CBS from ref 39			CBS from ref 40		expt	ref	
torsion barrier (internal rotation)	4.592			4.615		5.73	3	
inversion barrier	1.613			1.587		3.54	4	
						1.523	2	
						1.52	3	

^a All energies in this article have been transformed from the atomic units into kcal/mol using relation: 1 Hartree = 627.500 kcal/mol.

TABLE 4: C_a–N Bond Length in Å in Torsion Saddle Point, Ground State, and Inversion Saddle Point and Imaginary Frequencies of the Saddle Points (cc-pVTZ, HF/MP2)

	torsion saddle point	ground state	inversion saddle point	imaginary frequency in torsion saddle point (cm ⁻¹)	imaginary frequency in inversion saddle point (cm ⁻¹)
2-AP	1.427	1.369	1.357	375.85	345.34
4-AP	(cis)	1.428	1.372	325.96	358.76
	(trans)	1.429	1.372	367.42	358.76
5-AP	1.43	1.387	1.366	251.52	461.00
aniline	1.44	1.401	1.376		

In the torsion saddle point the symmetry group of the 2-AP, 4-AP, 5-AP, and aniline molecules is C_s , and the plane of symmetry is the aromatic ring plane. The C_a–N bond is in this plane, and the amino group hydrogen atoms are situated in symmetrical positions out of this plane. The presence of this symmetry allows optimization of the geometry in the saddle point without rolling down to the ground state. The amino group rotation in the 4-AP molecule can result in two different saddle points with “cis” and “trans” positioning to the neighbor ring nitrogen atom (see Table 1).

The 5-NP molecule has the same two planes of symmetry in the saddle point as in the ground state, but the oxygen atoms belong to the symmetry plane, which is perpendicular to the aromatic ring plane. In the course of the saddle point optimization with C_{2v} symmetry, the oxygen atoms cannot leave the plane of symmetry, thus preventing rolling down to the ground state.

Calculation of the energy in the inversion saddle point has been carried out with planar geometry of the molecules. The symmetry group of this state (C_s for the 4-AP and C_{2v} for the 2-AP, 5-AP, and aniline) implies presence of a plane of symmetry, which coincides with the aromatic ring plane. Geometry optimization imposing C_s or C_{2v} symmetry in the saddle point does not allow displacement of the amino group hydrogen atoms out of the symmetry plane.

Results and Discussion

The molecule of aminopyrimidine includes the aromatic ring containing the two nitrogen atoms, which have an electron withdrawing influence on groups situated in para and ortho positions (respectively for the 2-AP and the 4-AP). This effect

can be rationalized in terms of valence bond theory as a strong mixing of charge-transfer resonance structures 3 and 4 with main structures 1 and 2 (Figure 2). Mixing of structures 3 and 4 may govern the properties of aminopyrimidines in a number of ways. The C_a–N bond obtains “partially double” bond character, resulting from the amino group nitrogen lone pair delocalization through charge transfer to the aromatic ring nitrogen atoms (structures 3 and 4). Hence, the C_a–N bonds in the 2-AP and the 4-AP must be notably shorter than in the carbocyclic analogue (aniline) or the 5-AP molecule. The torsion barriers must be higher, whereas the amino group inversion barriers must be lower, and the amino group must be flatter, relative to the aniline or the 5-AP, or completely planar.

The same effects can be also described in another way as follows. There are two ways for the p lone pair of the amino group nitrogen to lower its energy. One is to make a hybrid orbital with the s orbital, which results in an sp³-like pyramidal amino group. The other is to share electrons with the aromatic ring through resonance structures such as 3 and 4. This results in the flat NH₂ group with an sp² nitrogen and a relatively short C_a–N bond of “partially double” character. The exact balance of these processes is subtle and depends on the possibility of forming resonance structures. There is a strong interaction between the aromatic ring and the NH₂ lone pair in the ground state and especially in the inversion saddle points of the 2-AP and the 4-AP because the lone pair and the orientation of the aromatic are almost collinear. On the other hand, the lone pair of amino group nitrogen and aromatic π system atoms are orthogonal in the torsion saddle point. This geometry cancels the resonance interaction, shifting the geometry of the NH₂ group to pyramidal sp³ with a relatively long C_a–N bond. Changing ground states with sp²-like amino nitrogen to inversion

TABLE 5: Torsion and Inversion Barriers (in kcal/mol) of the Studied Molecules^a

		HF	MP2	MP3	CISD	CISD(Q)	MP4	QCISD	QCISD(T)	CCSD	CCSD(T)	extrapolation	
												ref 39	ref 40
2-AP	torsion barrier											12.799	12.86
	cc-pVDZ/optDZ	13.108	11.34	11.194	12.522	12.113	11.128	11.554	11.266	11.346	11.188		
	cc-pVDZ/optTZ	12.947	11.353	11.171	12.455	12.055	11.129	11.545	11.277	11.335	11.199		
	cc-pVTZ/optTZ	13.748	12.362	12.349	13.579	13.207	12.204	12.644	12.406	12.468	12.329		
	inversion barrier											0.289	0.278
	cc-pVDZ/optDZ	0.165	0.785	0.718	0.335	0.466	0.919	0.711	0.856	0.742	0.869		
4-AP	cc-pVDZ/optTZ	0.318	0.721	0.675	0.415	0.505	0.819	0.672	0.775	0.693	0.783		
	cc-pVTZ/optTZ	0.021	0.395	0.318	0.077	0.159	0.478	0.337	0.419	0.349	0.426		
	torsion barrier (cis)											8.98	9.021
	cc-pVDZ/optDZcis	9.109	7.551	7.454	8.629	8.277	7.491	7.813	7.589	7.621	7.508		
	cc-pVDZ/optTZcis	8.991	7.55	7.418	8.584	8.232	7.472	7.795	7.582	7.599	7.5		
	cc-pVTZ/optTZcis	9.841	8.429	8.537	9.669	9.338	8.476	8.836	8.643	8.67	8.564		
	torsion barrier (trans)											12.531	12.576
	cc-pVDZ/optDZtrans	13.286	11.586	11.409	12.728	12.332	11.395	11.754	11.49	11.571	11.414		
	cc-pVDZ/optTZtrans	13.148	11.61	11.404	12.681	12.297	11.43	11.777	11.537	11.587	11.458		
	cc-pVTZ/optTZtrans	13.658	12.044	12.215	13.476	13.113	12.131	12.523	12.287	12.364	12.212		
	inversion barrier											0.349	0.336
	cc-pVDZ/optDZ	0.187	0.937	0.868	0.402	0.555	1.077	0.851	1.017	0.884	1.033		
cc-pVDZ/optTZ	0.379	0.858	0.812	0.501	0.604	0.961	0.802	0.918	0.824	0.928			
cc-pVTZ/optTZ	0.022	0.472	0.389	0.099	0.193	0.559	0.404	0.5	0.416	0.508			
5-AP	Torsion barrier											3.83	3.844
	cc-pVDZ/optDZ	1.752	4.586	3.438	2.856	2.95	3.752	3.131	3.39	3.103	3.352		
	cc-pVDZ/optTZ	1.453	4.618	3.402	2.72	2.841	3.761	3.096	3.391	3.067	3.353		
	cc-pVTZ/optTZ	1.72	4.992	3.658	2.971	3.092	4.165	3.323	3.718	3.318	3.695		
	Inversion barrier											1.396	1.372
	cc-pVDZ/optDZ	2.301	1.762	2.129	2.042	2.114	2.293	2.36	2.417	2.355	2.423		
Aniline	cc-pVDZ/optTZ	2.182	1.684	1.978	1.931	1.987	2.107	2.161	2.203	2.157	2.206		
	cc-pVTZ/optTZ	1.731	1.096	1.428	1.437	1.477	1.515	1.65	1.629	1.63	1.626		
	Torsion barrier											4.592	4.615
	cc-pVDZ/optDZ	3.982	4.193	3.797	4.128	4.005	3.966	3.868	3.873	3.782	3.843		
	cc-pVDZ/optTZ	3.845	4.208	3.771	4.072	3.956	3.965	3.852	3.873	3.763	3.842		
	cc-pVTZ/optTZ	4.262	4.71	4.29	4.585	4.477	4.5	4.342	4.406	4.272	4.379		
5-NP	Inversion barrier											1.613	1.587
	cc-pVDZ/optDZ	1.71	2.456	2.494	1.928	2.129	2.724	2.528	2.72	2.557	2.727		
	cc-pVDZ/optTZ	1.871	2.347	2.417	1.991	2.147	2.602	2.448	2.598	2.471	2.604		
	cc-pVTZ/optTZ	1.3	1.671	1.712	1.341	1.478	1.91	1.789	1.891	1.796	1.892		
	Torsion barrier											4.815	4.852
	cc-pVDZ/optDZ	9.128	4.313	5.707	7.492	6.988	5.132	6.051	5.664	5.984	5.72		
cc-pVDZ/optTZ	9.083	4.299	5.683	7.454	6.95	5.067	5.982	5.597	5.926	5.656			
cc-pVTZ/optTZ	8.201	3.688	5.288			4.256	5.39	4.935	5.352	4.984			

^a The cc-pVXZ/optYZ means calculation in the cc-pVXZ basis set with geometry optimization using the cc-pVYZ basis set.

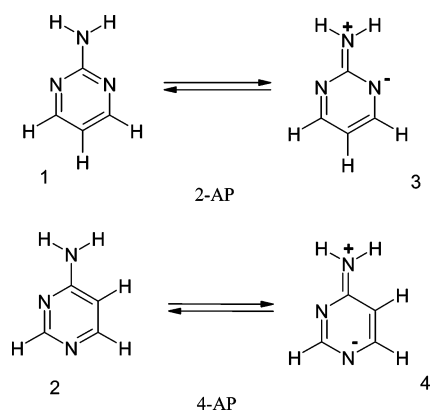


Figure 2. Possible resonance structures of the 2-AP and the 4-AP, which contribute to the wave function.

saddle point with complete sp^2 nitrogen requires significantly less energy than changing to torsion saddle point with sp^3 nitrogen with resonance interaction switched off.

Looking at the results of the calculations, presented in Tables 2–5, these qualitative predictions seem to be correct. The calculated parameters of the 2-AP and the 4-AP are similar, having a relatively flat (although not completely planar) amino group. The torsion barrier is higher, the barrier to inversion is lower and the C_a-N bond length is significantly shorter than

in aniline. The C_a-N bond length changed as expected:

$$C_a-N(\text{inversion saddle point}) < C_a-N(\text{ground}) < C_a-N(\text{torsion saddle point})$$

These tendencies described above are somewhat exaggerated by the HF calculations, but even the simplest correlated calculations (MP2) give very good results, close to the CCSD(T) values, although comparison with more advanced methods (CISD for example) show that good matching of the MP2 results may be from fortunate cancellation of errors. A priori, for arbitrary organic molecules, MP2 is not sufficient to obtain reliable results on rotational and inversion barriers heights.

The case of the 4-AP illustrates another source of torsional barrier. Two saddle point geometries were realized during the NH_2 group rotation. The conformation of the first saddle point (“trans”) is characterized by repulsive close positioning of the lone pair of the NH_2 group nitrogen and the aromatic nitrogen atom, whereas the possible attractive interaction between the amino group hydrogen atoms and the aromatic nitrogen atom is absent. The second conformation (“cis”) implies the close position of the hydrogen atoms of the amino group with the ring nitrogen atom. In this case repulsion of the lone pair of the amino group and the ring nitrogen atoms does not take place. As a result, the torsion barrier height in the 4-AP “cis” position

TABLE 6: Barrier Heights (in kcal/mol) of the Studied Molecules, Calculated by the DFT Method (B3LYP, cc-pVTZ Basis Set)

	2-AP	4-AP	5-AP	Aniline	5-NP
torsion barrier	14.52	10.68 (cis) 14.30 (trans)	5.53	5.78	5.18
inversion barrier	0.05	0.11	0.69	0.93	

is 4 kcal/mol lower than the heights for the 4-AP “trans” position or the 2-AP molecule, where repulsive interaction of nitrogen lone pairs also takes place at torsional saddle point geometry (see Table 5).

For the 5-AP, the resonance structures of type 3 and 4 are not favorable (even less favorable than in aniline), because in these structures the charge transfer occurs to the aromatic carbon lacking the electron-acceptor properties. That is why we can expect the trend opposite to the 2-AP and the 4-AP: a low NH₂ torsion barrier, a high NH₂ inversion barrier, and relatively long C_a–N bond. HF once again greatly overestimates this tendency (Table 5), ruled out from simple chemical intuition, whereas the correlated calculation gives results much closer to the corresponding values for aniline. The example of the 5-AP clearly shows that HF and simple correlated methods such as MP2 or CISD cannot produce meaningful results, although the Davidson correction always shifts the results of CISD in the right direction, possibly by taking into account higher quadruple excitations. The theory at the CCSD or QCISD level is needed, and the inclusion of perturbative triples also gives a notable correction. The difference between CCSD and QCISD methods is small. This is the result of the negligible contribution of singles in CCSD or QCISD wave functions, if canonical HF orbitals are used as reference (at the level of only doubles, CC and QCI are identical).⁴¹

From the practical point of view, the 5-AP represents a difficult case, when HF or simple correlated methods completely failed. To clarify if this situation is unique for amino-substitution, we calculated the barrier for inner rotation in another 5-substituted pyrimidine, namely 5-nitropyrimidine (5-NP). Despite the completely different nature of the substituent, the results are similar to the 5-AP, necessitating the inclusion of correlation at a high level.

The basis sets we employ are only small and medium sized, so extrapolation to complete basis set (CBS) is highly desirable. We used the procedure of Truhlar,^{39,40} specially parametrized to extrapolate from cc-pVDZ and cc-pVTZ results. The CBS approximated values are presented in Table 5. From the comparison of the CBS and cc-pVTZ energies it is clear that basis set incompleteness can be a serious source of error in torsional/inversion barrier heights determination. From this point of view, all results produced at the HF/MP2 level and/or with small basis sets can match the experimental results only because of fortunate cancellation of errors. On the other hand, it seems that the level of geometry optimization is not crucial for such calculations, as can be seen from comparison of results from optimizations in cc-pVDZ and cc-pVTZ basis sets (Table 5).

We find that the utility of DFT methods in calculation of inner motion barriers is questionable. As it clear from comparison of data from Tables 6 and 5, MP2/HF and even simple HF calculations give better estimations of CCSD(T)/CBS results than the popular DFT/B3LYP.

The validity of our calculations can be justified by comparison of the calculated (at the CCSD(T) theory level, CBS extrapolated) barriers for the aniline with experimental data^{2–4} (Table 3). The calculated inversion barriers match the experimental values very well. The calculated barrier to inner rotation of NH₂

group is also reasonable, although the comparison to experiment is ambiguous in this case, due to uncertainty of the experimental value.

Conclusions

The barriers for the amino group internal rotation and inversion were calculated for the 2-AP, 4-AP, and the 5-AP molecules. In the 2-AP and the 4-AP, the inversion barrier (≈ 0.3 kcal/mol) is much lower than the torsion one (≈ 12.5 kcal/mol for the 2-AP and trans saddle point of the 4-AP or ≈ 9.0 kcal/mol for cis saddle point of the 4-AP). The inversion barrier in the 5-AP (≈ 1.4 kcal/mol) is much closer to the torsion one (≈ 3.8 kcal/mol), and these barriers are near the respective values in aniline. These regularities can be explained qualitatively in the frame of valence bond theory consideration. The final barrier heights calculated by the CCSD(T) method with extrapolation to the complete basis set are presented in Table 4. Our calculations of the aniline by these methods are in good agreement with experimental data: calculated bond length is equal to experimental value to within 0.01–0.02 Å, and precision of angle value is up to 0.1–4°.

We have shown that HF or HF/MP2 and CISD calculations are insufficient to guarantee correct results for an arbitrary molecule. The CCSD theory levels are better, but the contributions from triples are not negligible (up to 0.4 kcal/mol, with this difference growing while the basis set increases), so the rather computationally expensive CCSD(T) theory is preferred. QCISD and QCISD(T) give virtually the same results as CCSD and CCSD(T), respectively. The MP3 and MP4 methods give acceptable results, but it was shown that MPn series generally do not converge to true correlation energy, so the utility of high order MP methods is questionable. The DFT based methods also cannot be recommended for such kinds of calculations. Because the calculations for these relatively large molecules can be performed with only basis sets of modest size (up to cc-pVTZ), the extrapolation to the infinite basis set is needed to avoid relatively large basis set truncation errors (up to 0.5 kcal/mol). Comparison of the calculated and experimental values for NH₂ group inversion and inner rotation barriers in aniline prove the validity of our calculations.

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