

Effects of Through-Bond Electron Donor–Acceptor Interaction on the Nitrogen Inversion Potential in Piperidine Derivatives. A Quantum-Chemical Study

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Ab initio and semiempirical quantum-chemical calculations indicate that the energy surface for inversion of the amino group in piperidine is drastically modified by the presence of electron acceptor groups in the 4-position of the ring. The efficiency of through-bond interaction (TBI) between the nitrogen donor and the electron acceptor depends strongly on the conformation. Along the nitrogen inversion pathway, stabilization occurs in particular in the region between the transition state and the axial conformer, whereas the equatorial conformation is less influenced by TBI. Semiempirical calculations do not appear useful in assessing through-bond interaction. Low-level ab initio Hartree–Fock calculations (3-21G basis set) are a much more sensitive probe of the effects of TBI, but their accuracy is questionable. The effects of TBI appear smaller when a more extensive basis set (6-31G*) is used, but electron correlation amplifies them again. The calculations corroborate experimental findings concerning the effects of through-bond interaction on molecular structure and energetics, although the agreement between theory and experiment is not quantitative.

1. Introduction

The conceptual distinction between through-space and through-bond interaction was developed on the basis of molecular orbital (MO) theory by Hoffmann and co-workers around 1970.^{1–3} Through-bond interaction (TBI) between functional groups—modeled as π -type or lone pair-type basis orbitals—through the σ -framework was shown to depend strongly on conformation: it is most effective in an all-trans orientation as sketched in Figure 1, part a.^{1–5}

In the case of 1,4-interactions in six-membered rings, this all-trans conformation cannot be attained, but calculations as well as experiments demonstrate that sizeable through-bond interactions exist in cis conformations (the well-known 1,4-diazabicyclooctane case, Figure 1 part b⁶) and in gauche conformations, provided that the lone pair orbitals are properly aligned with the central σ -bonds (e.g. piperazine with both N–H bonds axial but not equatorial,⁷ Figure 1, part c). In these cases TBI leads to a large splitting of the energies of the two highest doubly occupied MOs which can be characterized as the antisymmetric ($n-$, HOMO-1) and symmetric ($n+$, HOMO) combinations of the “lone pair” basis orbitals. Experimentally, this splitting can be observed by means of photoelectron spectroscopy.^{6,7} Characteristic for the predominance of through-bond over through-space interaction across an odd number of σ bonds is the level ordering symmetric > antisymmetric, which can be

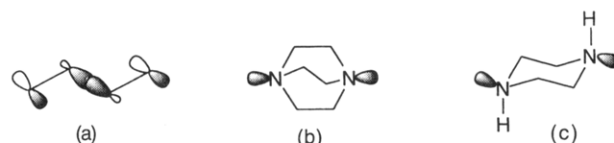


Figure 1. Typical orbital alignments for through-bond interaction: (a) optimal trans orientation, (b) dabco, (c) piperazine with hydrogens axial.

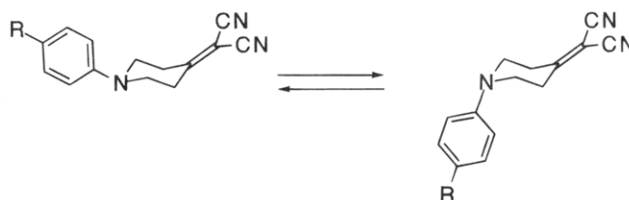


Figure 2. Conformational equilibrium in 1-phenylpiperidone derivatives **1** (refs 8, 9, and 10).

explained as a result of the mixing of the combinations of lone pair basis functions with σ and σ^* , respectively.

When the interacting orbitals are doubly occupied, their splitting does not have a large overall energetic effect. A different situation can arise when TBI involves an electron donor MO (e.g. the lone pair orbital on an amino nitrogen) and an empty low-lying electron acceptor MO. In such a case there can be a significant stabilization of the doubly occupied HOMO by the interaction with the unoccupied MO. Moreover, effects on the molecular geometry can be anticipated in this case because structural changes that optimize TBI can lower the total energy. In this paper we will study structural and energetic effects of TBI in piperidines carrying an electron accepting group at the 4-position, which are closely related to systems (e.g. **1**, Figure 2) studied experimentally in our laboratory.^{8–10} In these systems TBI mani-

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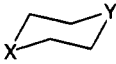
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Chart 1



Y =	CH ₂	C=CH ₂	C=O	C=C(CN) ₂	C=NH ₂ ⁺	CH ⁺
X=HN	2	3	4	5	6	7
X=MeN	8	9	10	11	12	13
X=CH ₂		14	15	16	17	18

feats itself in a strong charge-transfer band¹¹ in the UV/vis absorption spectrum, which is more intense in the axial than in the equatorial conformer.

In their early extended Hückel studies on the 4-piperidyl carbenium ion, Gleiter, Storer, and Hoffmann³ predicted that TBI should lead to (1) pyramidalization of the π -acceptor at C-4 and (2) an increase in the length of the central C-C bonds (C₂-C₃ and C₅-C₆). Indeed such geometric effects have been observed in the crystal structures of systems **1** and related compounds.^{9,10}

An energetic consequence of TBI in acceptor-substituted piperidines is that the conformer with the substituent in the axial position should be stabilized relative to the equatorial conformer. This phenomenon has been experimentally demonstrated in compounds **1**, in which up to 49% of the axial conformation is present at equilibrium in solution.¹⁰ The simplest representative of the series, **1** (R = H), even crystallizes with the phenyl group in an axial conformation.⁸⁻¹⁰

The model systems in the present computational study (Chart 1) are piperidine (**2**) and *N*-methylpiperidine (**8**), incorporating π -electron acceptors at the 4-position of the ring (compounds **3-7** and **9-13**). The substituents differ in their electron accepting ability, so that the strength of the electron donor acceptor interaction can be varied. In the molecules that have been studied experimentally, a phenyl ring is present. Replacement of this by hydrogen or methyl reduces the size of the computational problem so that ab initio models can be applied, but it should also allow for a more straightforward analysis of orbital interactions. Semiempirical AM1 and ab initio Hartree-Fock and MP2 methods are employed to investigate the structural and energetic consequences of TBI in the axial and equatorial conformers and the transition state linking them. The computational results will be compared with experiment in order to test their validity and to find out whether a modest level of semiempirical or ab initio theory can serve as a "model chemistry"¹² with a predictive value for the geometric and energetic effects of TBI. An analysis of the orbital interactions involved will be presented separately.¹³

2. Computational Methods

Semiempirical AM1 calculations were performed using the MOPAC program¹⁴ versions 5.0 and 6.0 or with Gaussian92.¹⁵ Transition states were located using the SADDLE algorithm in MOPAC. Configuration interaction in MOPAC involved the three highest occupied MOs

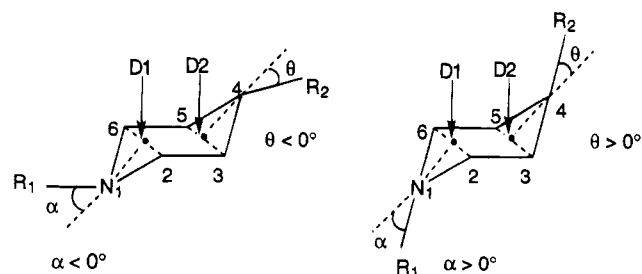


Figure 3. Definition of the dummy atoms D1 and D2 (D1 lies halfway between C2 and C6, D2 between C3 and C5) and the modes of pyramidalization at C4 ($\theta = 0^\circ$ if the angle R2-C4-D2 = 180°) and N1 ($\alpha = 0^\circ$ if the angle R1-N1-D1 = 180°).

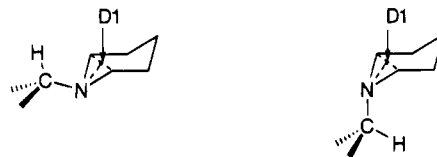


Figure 4. Schematic representation of the optimized rotamers for the *N*-methylpiperidine derivatives; dihedral angle H-C-N-D1 = 0° .

and the two lowest virtual orbitals and six electrons. For Hartree-Fock (HF) ab initio calculations, the programs Gaussian90 and Gaussian92¹⁵ were used with the standard 3-21G and 6-31G* basis sets. In order to account for electron correlation, Møller-Plesset perturbation theory (MP2) was applied (6-31G* basis set), with frozen core except for the geometry optimizations of **2**, **6**, and **7** which were performed with full MP2.

The conformation of the piperidine ring (confined to C_s symmetry) as well as the pyramidalization angles α and θ is conveniently defined with the aid of the dummy atoms D1 and D2, see Figure 3.

The energies and structures as a function of the NH orientation angle α were studied by stepwise variation of α from one value to another with full optimization of the remaining degrees of freedom. The nitrogen inversion process in *N*-methylpiperidine is complicated because it is coupled to a rotation of the methyl group (cf. Figure 4), which breaks the C_s symmetry. In this case we studied only the axial and equatorial conformers. A schematic representation of the C_s rotamer of the *N*-Me group (dihedral angle H-C-N-D1 = 0°), used throughout the calculations on the equatorial and axial conformations of the *N*-methylpiperidine derivatives, is given in Figure 4.

All HF-optimized structures were characterized as either minima or transition states by a normal mode calculation. Unfortunately, at the MP2 level the geometry optimizations of the larger model compounds and vibrational analyses are too expensive in CPU time or disk usage to be feasible on the computer facilities available to us. The ab initio transition state optimizations succeeded only when the Hessian matrix was explicitly calculated, which could only be done at the HF

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Table 1. Energies of N-H Systems 2-7^a

	AM1	AM1/CI	3-21G	6-31G*	MP2/6-31G*	MP2/6-31G*
2-eq	-19.04	-19.45	-248.80326	-250.18871	-251.00163	-251.03088
2-TS	4.03		3.01	6.12	6.68	
2-ax	-2.73	-2.63	0.32	0.82	0.51	0.60
3-eq	4.64		-286.43716	-288.03541	-288.96860	
3-TS	4.02		2.73	5.93	6.31	
3-ax	-2.76		0.15	0.69	0.26	
4-eq	-43.80		-322.07805	-323.88642	-324.86165	
4-TS	3.68		2.50	5.84	6.16	
4-ax	-2.53		0.29	0.94	0.42	
5-eq	67.61	64.02	-468.87324	-471.50214	-472.98387	
5-TS	3.56		2.11	5.47	5.64	
5-ax	-2.43	-2.61	0.36	0.99	0.39	
6-eq	151.52	151.48	-302.74314	-304.42857	-305.38045	-305.41471
6-TS	1.55		0.79	4.02	3.49	
6-ax	-1.61	-1.66	0.62	1.76	0.66	0.51
7-eq	193.83	193.74	no minimum	-249.31587	-250.09603	-250.12574
7-TS	1.46		no TS	1.22	-7.40	
7-ax	-1.50	-5.87	-247.94483 ^b	-2.81	-15.59	-17.63

^a For the equatorial conformers the AM1 heat of formation (kcal/mol) or ab initio total energy (hartrees) is given. For the axial conformers and N inversion transition states the energies (ΔE , kcal/mol) are relative to the equatorial form. Frozen core MP2 was used, except for the geometry optimizations of **2**, **6**, and **7**. MP2(frozen core) energies for **2-ax**/eq: -251.00208/-251.00298 hartree. ^b For **7-ax** (3-21G) the absolute energy is reported.

Table 2. Geometric Features for the N-H Systems 2-7^a

	AM1			3-21G			6-31G*			MP2/6-31G*	
	eq	TS	ax	eq	TS	ax	eq	TS	ax	eq	ax
	Bond Length (Å)										
2	1.528	0.005	0.002	1.535	0.007	0.007	1.528	0.004	0.005	1.523	0.006
3	1.530	0.006	0.003	1.542	0.009	0.009	1.531	0.006	0.007		
4	1.527	0.007	0.003	1.542	0.011	0.012	1.532	0.008	0.009		
5	1.531	0.008	0.004	1.547	0.012	0.014	1.534	0.009	0.010		
6	1.538	0.013	0.011	1.562	0.022	0.028	1.541	0.016	0.019	1.546	0.033
7a	1.536	0.022	0.062				1.533			1.528	
7b	1.536 ^b		0.117 ^b			1.748	1.611	0.021	0.057		1.762
	Pyramidalization Angle α (degrees)										
2	-51.7	-3.2	53.2	-44.9	3.7	47.0	-51.3	4.1	52.7	-54.3	56.0
3	-51.7	-3.6	52.7	-44.4	2.7	46.3	-51.4	3.4	52.1		
4	-51.2	-4.3	51.8	-43.9	2.4	44.5	-51.4	3.0	51.0		
5	-51.0	-4.4	51.4	-42.3	2.6	42.6	-50.7	3.2	50.2		
6	-46.1	-8.3	43.8	-34.4	4.1	26.0	-47.6	3.3	43.1	-49.3	44.6
7a	-46.1	-13.4	33.3				-47.2			-49.2	
7b	-46.0 ^b		28.1 ^b			23.3	-38.5	-19.0	37.6		30.7
	Pyramidalization Angle θ (degrees)										
3	-1.2	-0.9	-0.9	1.7	2.3	2.2	1.5	1.7	1.9		
4	-1.6	-1.2	-1.1	-0.1	0.5	0.7	-0.6	-0.1	0.2		
5	-1.7	-1.3	-1.3	2.5	3.6	3.5	0.9	1.5	1.6		
6	-1.3	0.3	0.8	1.8	4.1	4.6	0.2	2.0	2.6	3.5	7.8
7a	-1.5	1.2	7.5				-4.8			-4.3	
7b	-1.4 ^b		10.9 ^b			13.8	13.8	14.1	14.8		17.3

^a Bond lengths r_{CC} (Å) for the equatorial conformer, relative bond lengths for the TS and the axial form. Pyramidalization angles α and θ as defined in Figure 3. For structures **7a** and **7b**, see Figure 5. ^b AM1/CI results for **7a**, not **7b**.

level. Corrections for zero-point vibrational energy are not reported because the differences in ZPVE between the isomers turned out to be small (< ca. 0.05 kcal/mol).

3. Results

3.1. N-H Systems. In Table 1 we present the results on the N-H systems **2-7**: the energies of the equatorial conformer and the relative energies of the inversion transition states and the axial minima. The key geometric features are presented in Table 2: the C₂-C₃ (= C₅-C₆) bond length and the angles α and θ which characterize the orientation of the N-H bond and the pyramidalization at the acceptor side (Figure 3). Note that a positive value of α or θ corresponds to an axial disposition of the substituent.

The vibrational analyses revealed that the axial and equatorial forms were true minima except in the case of **7**, as discussed below. The transition states for N

inversion all had one normal mode with an imaginary frequency. With the carbenium ion **7**, some complications arise. A stationary point with C_s symmetry corresponding to the axial conformer **7-ax** could be located at all levels of theory. In **7-ax** the acceptor part adopts a "puckered" conformation (angle D1-D2-C4 \approx 113°, except with AM1, see below), analogous to that of the cyclohexyl carbenium ion **18b** (see below). For the equatorial form **7-eq**, the results depend strongly on the level of theory. With the 3-21G basis set, no equatorial minimum could be found at all: there is no barrier along the pathway toward the axial form. With the 6-31G* basis set, there are two shallow local minima, one with a flattened ring shape (angle D1-D2-C4 \approx 165°) analogous to **18a** (**7-eq-a**) and another (**7-eq-b**) with the "puckered" conformation, see Figure 5. Inclusion of MP2 electron correlation leaves only **7-eq-a** as a local minimum (cf. Figure 8, below). According to AM1 calculations, **7-eq** can only attain the "flat" conformation (angle D1-D2-

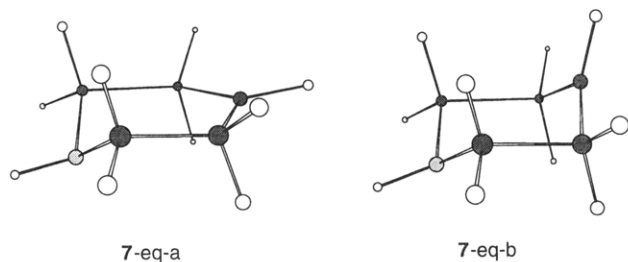


Figure 5. HF/6-31G* optimized structures of the equatorial 4-piperidyl carbenium ion, with the "flat" (7-eq-a) and "puckered" (7-eq-b) ring shapes.

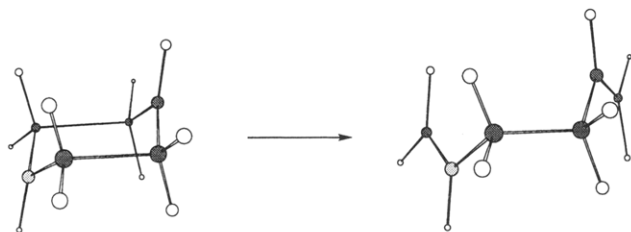


Figure 6. Lowering of the symmetry of 7-ax and subsequent geometry optimization (3-21G level) leads to spontaneous Grob fragmentation.

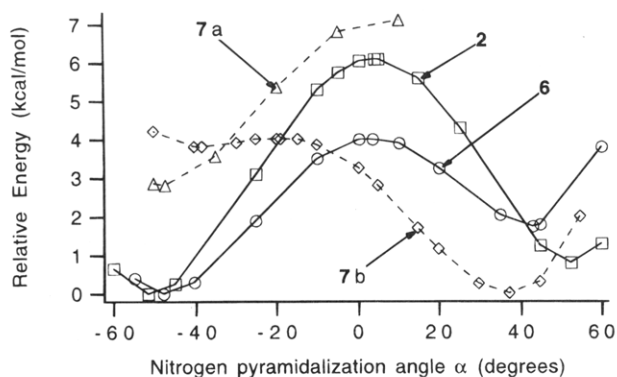


Figure 7. Relative energy (6-31G*) along the nitrogen inversion pathway for piperidine (**2**) (squares), 4-iminiumpiperidine (**6**) (circles), and the carbenium ion **7** in its two forms, "flat" (**7a**, triangles) and "puckered" (**7b**, diamonds).

C4 \approx 169°), whereas the axial form has a fairly normal ring shape (D1–D2–C4 \approx 130°).

With the 3-21G basis set, 7-ax is not a true minimum. There is one vibrational mode with a negative force constant, and full geometry optimization after slight lowering of the symmetry resulted in a spontaneous Grob fragmentation,¹⁶ cf. Figure 6. In contrast, with the 6-31G* basis set, 7-ax is a true minimum with only positive force constants.

The pathway of nitrogen inversion was followed by varying the pyramidalization angle α and optimizing the other degrees of freedom within the C_s point group. Selected plots of energies and the C₂–C₃ bond length as a function of α are presented in Figures 7–9.

3.2. N-Me Systems 8–13. The trialkylamino group in **8** is a better electron donor than the secondary amine in **2**, as reflected by the experimental ionization potentials of 8.37 and 8.70 eV, respectively.¹⁷ The absolute energies of equatorial conformers and the relative energies of the axial conformations are given in Table 3. The

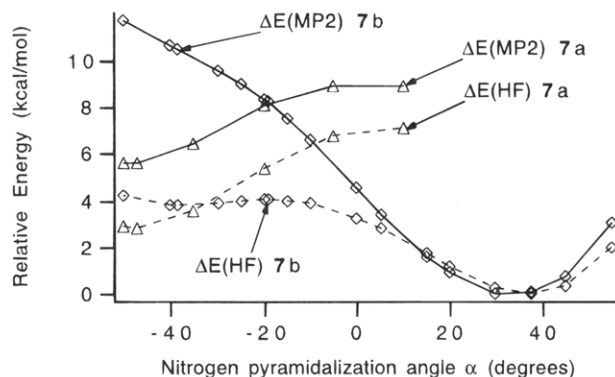
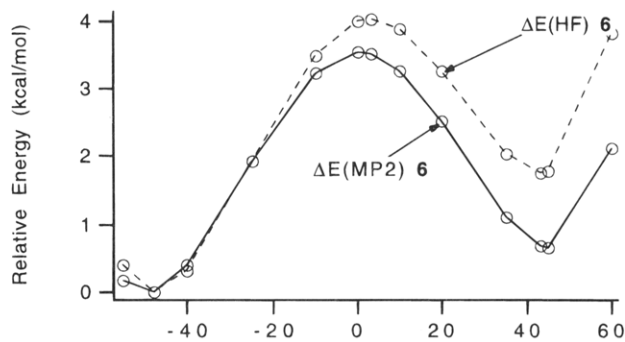


Figure 8. Effect of electron correlation on the inversion potential in **6** and **7**. Top: HF/6-31G* (dashed) and MP2/6-31G*//6-31G* (full line) curves for **6**. Bottom: HF/6-31G* (dashed) and MP2/6-31G*//6-31G* (full line) curves for the carbenium ions **7a** (triangles) and **7b** (diamonds).

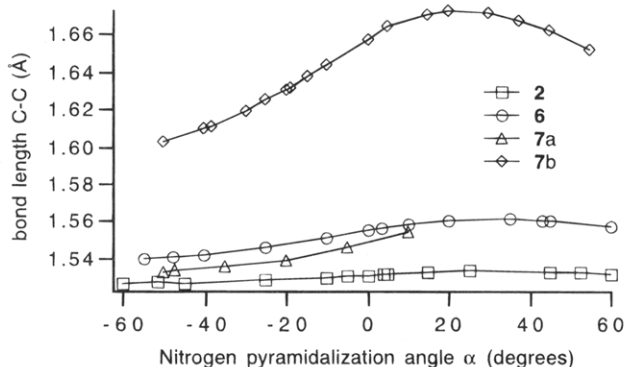


Figure 9. Length of the C₂–C₃ (= C₅–C₆) bond as a function of pyramidalization angle α (6-31G*) for **2**, **6**, and **7** in its flat and puckered forms.

characteristic pyramidalization angles α and θ and the C₂–C₃ bond lengths are presented in Table 4.

For the carbenium ion **13**, 3-21G calculations reveal a "flat" equatorial conformation (D1–D2–C4 = 157°) as a true minimum, in contrast to the situation of the analogous N–H system **7**. For the axial form, the C_s minimum is actually a transition state: the first normal mode (312i cm⁻¹) clearly corresponds with the onset of a Grob fragmentation, which indeed occurs spontaneously upon geometry optimization with a lower symmetry. With the 6-31G* basis set, puckered and flat forms of **13**-eq are found, just as in the case of **7**.

3.3. Acceptor Reference Systems. In order to allow a comparison of the pyramidalization of the acceptor at C-4 and of the central C₂–C₃ (= C₅–C₆) bond length, the reference systems lacking the donor (**14**–**18**) were studied. In Table 5 we present the results for the energies E (hartree) or heat of formation (kcal/mol), the LUMO

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Table 3. Energies [Heat of Formation (kcal/mol) or Absolute Energy (hartree)] of Equatorial Conformers and Relative Energies (kcal/mol) of Axial Conformers for *N*-Me systems 8–13

	AM1	AM1/CI	3-21G	6-31G*	MP2/6-31G*
8-eq	-15.21	-15.47	-287.61856	-289.21933	-290.16585
8-ax	-1.41	-1.47	2.01	3.60	3.32
9-eq	8.49		-325.25225	-327.06582	-328.13259
9-ax	-1.48		1.63	3.29	2.74
10-eq	-39.97		-360.89299	-362.91660	-364.02520
10-ax	-1.39		1.35	3.07	2.36
11-eq	71.41		-507.68817	-510.53245	-512.14759
11-ax	-1.35		1.33	3.03	2.20
12-eq	154.83		-341.55810	-343.45900	-344.54405
12-ax	-1.15		0.72	2.79	1.14
13-eq ^a	197.04	196.98	-286.74209	-288.34635	-289.25962
13-ax ^b	-1.88	-4.82	-12.53	-3.03	-18.19

^a "Flat" conformation 13-eq-a; at the 6-31G* level the "puckered" form 13-eq-b exists as a second local minimum with $E = -288.34481$ au (relative energy +0.97 kcal/mol). ^b "Puckered" conformation 13-ax-b.

Table 4. Geometric features for the *N*-Me Systems 8–13^a

	AM1		3-21G		6-31G*	
	eq	ax	eq	ax	eq	ax
Bond Lengths (Å)						
8	1.527	0.003	1.535	0.009	1.526	0.008
9	1.529	0.004	1.541	0.011	1.530	0.010
10	1.526	0.004	1.541	0.015	1.531	0.012
11	1.530	0.004	1.545	0.017	1.533	0.013
12	1.536	0.013	1.558	0.033	1.540	0.023
13a	1.533	0.065	1.549		1.532	
13b	1.534 ^b	0.082 ^b		1.758	1.606	1.677
Pyramidalization Angle α (degrees)						
8	-45.9	45.2	-45.2	40.3	-48.1	42.8
9	-47.0	45.1	-45.0	39.9	-48.1	42.4
10	-46.5	44.7	-44.9	39.4	-48.3	42.0
11	-46.2	44.0	-44.1	38.5	-47.8	41.6
12	-44.0	38.9	-40.5	33.0	-46.4	37.9
13a	-44.8	31.4	-40.1		-46.2	
13b	-43.6 ^b	27.5 ^b		25.6	-40.2	32.9
Pyramidalization Angle θ (degrees)						
9	-1.2	-0.8	1.7	2.4	1.6	2.1
10	-1.5	-1.0	-0.3	0.7	-0.7	0.2
11	-1.7	-1.3	2.3	3.5	0.7	1.6
12	-1.3	0.9	1.5	4.6	0.3	2.8
13a	-1.7	7.6	-4.0		-5.0	
13b	-1.5 ^b	9.4 ^b		13.8	13.9	14.7

^a Bond lengths r_{CC} (Å) for the equatorial conformer, relative bond lengths for the axial forms. Pyramidalization angles α and θ as defined in Figure 3. ^b AM1/CI for 13a, not 13b.

energies (eV), the bond lengths $r(CC)$, and the pyramidalization angle θ .

The cyclohexyl carbenium ion **18** is found to have two distinct conformations of C_s symmetry (see Figure 10), one "flat" (**18a**) and the other strongly puckered (**18b**). Both are true energy minima at the HF and MP2 levels. The puckering angles D1–D2–C4 in **18a** and **18b** are 162° and 111° at the HF level, 165° and 106° at the MP2 level.

4. Discussion

4.1. Axial/Equatorial Energy Difference in Piperidine (2) and *N*-Methylpiperidine (8). The preferred conformation of piperidine (**2**) in solution has been a topic of debate for a long time,^{18,19} but it is now accepted that 2-eq is the most stable conformer with $\Delta G^\circ = 0.4 \pm$

0.2 kcal/mol in the gas phase and in nonpolar solvents.^{18–20} Surprisingly, the AM1 computations predict the axial conformer 2-ax to have a lower heat of formation than 2-eq by as much as 2.73 kcal/mol (cf. Table 1), which is obviously not a correct result. Even for *N*-methylpiperidine (**8**), the AM1 calculations predict the axial conformer 8-ax to be the most stable one by 1.41 kcal/mol, while experimentally 8-eq is more stable than 8-ax by about 3 kcal/mol.^{21–23} According to the AM1 results, the energy difference between 8-ax and 8-eq is reduced by 1.32 kcal/mol with respect to the calculated energy difference between 2-ax and 2-eq. In other words, the AM1 computations predict that the substitution of *N*-H by *N*-CH₃ results in a destabilization of the axial conformation of 1.32 kcal/mol, which is much less than the experimentally found value of ca. 2.6 kcal/mol. The ab initio calculations correctly predict 2-eq and 8-eq to be favored over 2-ax and 8-ax, respectively, and the calculated energy differences agree reasonably well with the experimental values. It is interesting to note that the preference of a methyl group for the equatorial position is considerably greater in piperidine than in cyclohexane, which is known from experiment and which is fully supported by our calculations and those of Wiberg and Murcko.²⁴

The nitrogen inversion barrier of piperidine has been determined by dynamic NMR²⁰ as $\Delta G^\ddagger = 6.1 \pm 0.2$ kcal/mol. The barriers computed with the 6-31G* basis set are in accord with this, while the AM1 and 3-21G barriers are too low.¹²

Although the energetic results of AM1 are not correct, the geometries appear quite reasonable (Tables 2 and 4; ref 10). The related semiempirical methods MNDO and PM3 do not have advantages over AM1 in this case. With MNDO the correct energy ordering is obtained, but the geometries are poor,^{10,25} while for *N*-methylpiperidine the results with PM3 are similar to the AM1 results.

Hyperconjugative interactions between the lone pair and the adjacent C–C and C–H bonds depend on the conformation. In the conformer with the methyl group in the favored equatorial position, the axial lone pair can interact with the axial C–H bonds of the neighboring methylene group. This leads to a lengthening of these bonds and to the occurrence of characteristic IR bands between 2700 and 2850 cm⁻¹, known as "Bohlmann bands".²⁶ The lengths of the C–H bonds of the α - and β -methylene groups and some relevant computed vibrational frequencies of *N*-methylpiperidine (**8**) are listed in Table 6.

We have found that the axial C–H bond of the α -methylene groups (C_2 , C_6) is longer than the equatorial one, but much more so in the conformer with the methyl group equatorial. The bond lengths of the β -CH₂ groups are quite insensitive to the axial or equatorial position of the methyl group. In this case the equatorial and axial bonds have almost the same length. According to all

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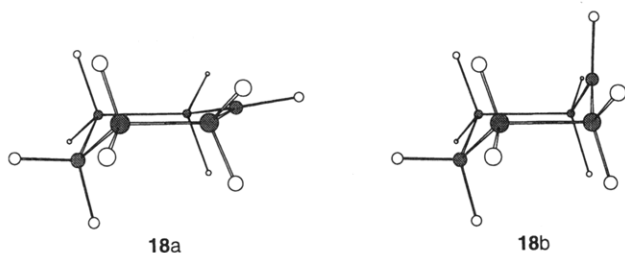
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Table 5. Properties of Reference Acceptor Compounds 14–18. Energies (hartree) [AM1 Heat of Formation (kcal/mol)], C–C Bond Length r_{CC} (Å), Pyramidalization Angle θ (degrees), and LUMO energy (eV)^a

		AM1	3-21G	6-31G*	MP2//6-31G*	MP2//6-31G*
14	<i>E</i>	-14.81	-270.55086	-272.05482	-272.95877	
	r_{CC}	1.517	1.547	1.536		
	θ	-1.1	1.6	1.3		
	LUMO	1.33		5.06		
15	<i>E</i>	-63.46	-306.19162	-307.90592	-308.85184	
	r_{CC}	1.514	1.547	1.537		
	θ	-1.4	0.1	-0.4		
	LUMO	0.92		4.37		
16	<i>E</i>	47.94	-452.98700	-455.52176	-456.97431	
	r_{CC}	1.518	1.551	1.539		
	θ	-1.6	2.4	0.9		
	LUMO	-0.75		1.96		
17	<i>E</i>	130.92	-286.85694	-288.44927	-289.37170	
	r_{CC}	1.520	1.561	1.545		
	θ	-0.6	2.1	0.8		
	LUMO	-5.59		0.79		
18a (flat)	<i>E</i>	174.12	-232.03923	-233.33551	-234.08620	-234.08791
	r_{CC}	1.516	1.549	1.535		1.529
	Φ	172.3	157.1	161.7		165.4
	θ	-1.8	-5.0	-6.1		-5.9
	LUMO	-7.16		-4.48		
18b (puckered)	<i>E</i>		-232.04482	-233.33552	-234.09260	-234.09517
	r_{CC}		1.634	1.601		1.629
	Φ		110.3	111.2		106.0
	θ		12.0	12.9		13.9
	LUMO			-4.22		

^a For the two conformations of **18**, the angle D1–D2–C4 = Φ (degrees) is also given (cf. Figure 3).

**Figure 10.** Two minimum energy structures of the cyclohexyl carbenium ion (MP2/6-31G*): **18a** (“flat”) and **18b** (“puckered”).**Table 6. Selected Computed Properties of *N*-Methylpiperidine (**8**) Related to Hyperconjugation of the Lone Pair with C–H Bonds: Bond Lengths (Å) of the C–H Bonds of the α - and β -Methylene Groups; Frequencies (cm^{-1} , not scaled) of the Symmetric and Antisymmetric C–H(ax) Stretching Vibrations of the α -Methylene Groups That Give Rise to Bohlmann Bands, and the Lowest Frequency among the Methyl C–H Stretching Modes**

	AM1		3-21G		6-31G*	
	8-ax	8-eq	8-ax	8-eq	8-ax	8-eq
$r(\alpha, \text{ax})$	1.1272	1.1305	1.0856	1.0940	1.0880	1.0972
$r(\alpha, \text{eq})$	1.1250	1.1262	1.0832	1.0833	1.0849	1.0849
$r(\beta, \text{ax})$	1.1211	1.1216	1.0853	1.0839	1.0877	1.0866
$r(\beta, \text{eq})$	1.1197	1.1207	1.0853	1.0850	1.0871	1.0867
$\nu(\alpha'')$	2986	2949	3192	3096	3189	3085
$\nu(\alpha')$	2988	2950	3197	3101	3195	3093
$\nu(\text{Me})$	2991	2986	3141	3116	3151	3125

calculations, the C₂–C₃ bond in the axial conformer is slightly longer than in the equatorial conformer. As far as the vibrations are concerned, the CH stretching modes of the axial hydrogens occur at higher frequency than the modes of the methyl group in the axial form, whereas the frequencies are clearly lower in the equatorial conformer. The frequencies are much easier to determine experimentally than the bond lengths and therefore are a useful test of the validity of calculations. In practice, the Bohlmann bands are found to be well separated from the “normal” C–H stretches. The mag-

nitude of the shift due to the hyperconjugative effect is at least about 100 cm^{-1} . The semiempirical AM1 model clearly underestimates this effect, whereas the ab initio results are satisfactory.

We conclude that the AM1 calculations are unsatisfactory in several respects. Nevertheless it is of interest to see whether they can properly describe trends in the effects of donor–acceptor interaction, because the semiempirical methods are at present still the most obvious way to study molecular systems which are too large for ab initio calculations.

4.2. Reference Acceptor Systems. In the series **3–7** and **9–13** the strength of the acceptor is increased, as illustrated by the LUMO energies of the reference acceptors **14–18** (Table 5). Cyclohexanone (**15**) and its methylene and dicyanomethylene derivatives **14** and **16** show no unusual geometric features. The C₂–C₃ bond lengths are essentially the same, and the pyramidalization of the acceptor is small. In the iminium ion **17** the central bond is lengthened by up to 0.01 Å, probably as a result of some donation of electron density from this σ -bond to the acceptor.

According to our ab initio calculations, the cyclohexyl carbenium ion has two distinct energy minima, **18a** and **18b** (cf. Figure 10). At the HF level the energy difference is small, but with electron correlation included the “puckered” conformation **18b** is 4.6 kcal/mol lower in energy. The flat conformation **18a** favors hyperconjugation of the carbenium ion center with the axial C–H bonds. As a result, the bond lengths of the axial CH bonds at C-3 are 1.12 Å whereas other C–H bond lengths in **18a** and **18b** are between 1.09 and 1.10 Å (MP2/6-31G*). The puckered conformation **18b** allows overlap of the LUMO with the central C–C bond, which results in a considerable lengthening of the C–C bond (1.63 Å at MP2/6-31G*) and a large positive pyramidalization of the C+ center. A similar deformation of the ring near the carbenium ion center has recently been found in a

Table 7. Energy Differences $\Delta\Delta E(\text{TS})$ and $\Delta\Delta E(\text{ax})$ (kcal/mol) of TS and Axial Forms Compared to Those of the Equatorial Conformer for *N*-H Systems 3–7 Relative to Piperidine (2) and $\Delta\Delta E(\text{ax})$ for the *N*-Methyl Systems 9–13 Relative to *N*-Methylpiperidine (8)^a

	AM1	AM1/CI	3-21G	6-31G*	MP2//6-31G*	MP2/6-31G*
3-TS	-0.01		-0.28	-0.19	-0.37	
4-TS	-0.35		-0.51	-0.28	-0.52	
5-TS	-0.47		-0.91	-0.65	-1.04	
6-TS	-2.48		-2.22	-2.10	-3.19	
7-TS	-2.57			-4.90	-14.08	
3-ax	-0.03		-0.17	-0.13	-0.25	
4-ax	0.20		-0.03	0.12	-0.08	
5-ax	0.30	0.02	0.04	0.17	-0.12	
6-ax	1.12	0.97	0.30	0.94	0.15	-0.09
7-ax	1.23	-3.24		-3.63	-16.09	-18.23
9-ax	-0.07		-0.38	-0.31	-0.58	
10-ax	0.03		-0.67	-0.53	-0.96	
11-ax	0.07		-0.68	-0.57	-1.12	
12-ax	0.27		-1.29	-0.81	-2.18	
13-ax	-0.46	-3.35	-14.54	-6.64	-21.51	

^a For explanation, see text.

computational study of the 2-adamantyl cation.²⁷ With the semiempirical AM1 method only the "flat" chair structure **18a** could be found. This kind of deformation of the chair conformation was also found in earlier semiempirical calculations.²⁸ Even though the AM1 method probably predicts an incorrect conformational preference, the computed heat of formation $H_f = 174.12$ kcal/mol agrees reasonably well with the reported experimental values of 179²⁹ and 177 kcal/mol.³⁰

4.3. Donor–Acceptor Systems. Trends in Axial/Equatorial Energy Differences. In the series **3–7** and **9–13** the strength of the acceptor is increased. As a result, increased effects of electron donor–acceptor interactions may be anticipated, leading among other things to a relative stabilization of the axial form.³ Taking the axial–equatorial energy difference ($\Delta E(\text{ax} - \text{eq})$) in piperidines **2** or **8** as a reference point, we can calculate the relative effects ($\Delta\Delta E(\text{ax})$) of variation of the 4-substituents on the energy of the axial conformer. Thus, a negative value of $\Delta\Delta E$ means that the axial form is stabilized relative to the reference system, a positive value is indicative of a destabilizing interaction. The same comparison can be made for the transition state ($\Delta\Delta E(\text{TS})$) in the case of the *N*-H compounds. The $\Delta\Delta E$ values are shown in Table 7.

Inspection of the results in Table 7 reveals some unexpected trends. For the *N*-methyl systems **9–13** at the ab initio level, the axial conformer is relatively stabilized more as the acceptor is made stronger, as expected for enhanced donor–acceptor (D/A) interaction, but for the *N*-H series **3–7** this is not the case. On the other hand, a clear stabilization of the TS structure upon increase of acceptor strength going from **3** to **7** is evident at the ab initio and AM1 levels. It must be concluded that the relative energies of the axial and equatorial conformers in the *N*-H series are not exclusively controlled by D/A interaction but also by other effects.

It is remarkable that the methylene group introduced in **3** and in **9** already has a significant effect on the

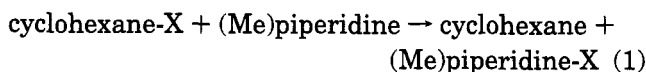
Table 8. Energies (kcal/mol) of Isodesmic Reactions^a (See Eq 1)

	3-21G	6-31G*	MP2//6-31G*
3-ax	-0.13	-0.06	-0.14
4-ax	-0.07	0.25	0.04
5-ax	0.11	0.37	0.16
6-ax	0.39	1.83	0.94
7-ax	-8.89	-3.40	-11.96
9-ax	-0.22	-0.10	-0.32
10-ax	-0.49	-0.13	-0.41
11-ax	-0.38	-0.17	-0.53
12-ax	-0.98	0.19	-1.01
13-ax	-15.30	-6.33	-21.00

^a Energies of cyclohexane (hartree): 3-21G, -232.91691; 6-31G*, -234.20801; MP2//6-31G*, -234.99162.

relative energies of the *N* inversion transition state and the axial conformers. Interestingly, significant effects on the stereochemistry of hydrogenation have recently been observed for the exocyclic double bond of piperidones and methylene derivatives.³¹ These were attributed to the interaction between the amino group and the double bond.

In order to assess the interactions between substituents, an isodesmic reaction approach can be used.¹² In Table 8 the computed energies of reaction are reported for the transfer of the acceptor group from cyclohexane to the donor–acceptor system (axial conformation):



A negative energy difference means that the interaction in the donor–acceptor system is favorable.

We have found that there are destabilizing interactions in the case of **4**, **5**, and **6** which parallel the $\Delta\Delta E(\text{ax})$ values (Table 7). We tentatively attribute these to dipole–dipole repulsions between the polar substituent and the *N*-H group. In the equatorial conformer of piperidine (**2**), the computed dipole moment is 0.96 D (6-31G*), in good agreement with experiment (0.82 D³²). For the axial conformer the dipole moment is greater, 1.28 and 1.19 D from calculation and experiment, respectively. For the transition state for *N* inversion, the computed dipole moment is 0.54 D. The balance between the stabilizing TBI and destabilizing dipole–dipole interaction determines whether the axial conformer will be relatively stabilized or destabilized. For **4** to **6**, a small overall destabilization is calculated (except at the MP2 level, see below). Introduction of the strong acceptor, in the carbenium ion **7**, increases TBI so much that a net stabilization of the axial conformer occurs. In the *N*-methyl series, the D/A interaction is enhanced due to the increased donor capacity of the trialkylamino group. Moreover, the calculated dipole moment for *N*-methylpiperidine (**8**) is smaller than that for **2**, viz. 0.60 in the equatorial and 0.88 D in the axial conformation, so the dipole–dipole repulsion will be less important. Thus, the trends in the interaction energy (Table 8) and the relative stabilization of the axial form (Table 7) conform to the expectation based on TBI. From the difference between the corresponding entries in Table 7 and Table 8, the isodesmic reaction energies for the equatorial conformations can be calculated. In most cases these are small, and positive, i.e. the interaction is slightly unfavorable.

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From Table 7 we also learn that the stabilizing effect is greater in the transition state for N inversion than in the axial conformation. This is further illustrated by Figure 7, which shows the inversion potential for **2**, **6**, and **7** at the HF/6-31G* level. The axial form (α 40–50°) is disfavored in **6** as discussed above, but the inversion barrier is lowered significantly. In **7** the barrier is almost absent as a result of the enormous stabilization of the axial conformation. The diminution of the barrier can be understood to be a result of stronger TBI in the TS because the donor–acceptor energy gap is smaller due to the low ionization potential of the amino group at the planar trigonal geometry.

4.3. Effect of Basis Set and Electron Correlation on Relative Energies. The results in Table 7 reveal that in the HF calculations with the small 3-21G basis set the differential stabilization of the axial conformation and the TS as a result of TBI is more pronounced than in the calculations with the more extended 6-31G* basis set or with the AM1 Hamiltonian. The importance of electron correlation in proper description of electron delocalization through (σ) bonds is well established.^{33–35} When a correlation correction is applied at the MP2 level (6-31G* basis set), large effects on relative energies are found. The energy differences at this level are even greater than those at the HF/3-21G level. The stabilization of the axial conformation is particularly large in the case of the extremely strong carbenium ion acceptor. In the iminium ions **6** and **12** and the neutral compounds, the importance of electron correlation tends to be greater as TBI is more important. In Figure 8 the dependence of the electron correlation correction on geometry is shown. Going from equatorial to axial (increasing α), the role of electron correlation gradually increases. This is most notable in the carbenium ion **7b**, in which the local equatorial minimum that was present at the HF/6-31G* level disappears.

In the semiempirical AM1 calculations, limited configuration interaction (CI) has an influence on the properties only in the case of the strongest donor–acceptor couples, that is in **7** and **13**. An effect on the calculated heat of formation is found in particular in the case of **7-ax**, which is stabilized by as much as 4.37 kcal/mol upon inclusion of CI, whereas **7-eq** is only stabilized by 0.09 kcal/mol (Table 1). Consequently, $\Delta\Delta E(\text{ax})$ for **7** is increased by 4.28 kcal/mol. This effect can be attributed to the mixing of the doubly excited HO²LU² configuration into the ground state CI expansion, which is significant only in this case. In all other cases, the energy of this configuration is so high that its role is negligible.

4.4. Comparison with Experiment. The energetic effects of donor–acceptor interaction, anticipated on qualitative grounds, are confirmed by the quantum-chemical calculations presented here. One reason to undertake this study was to find independent support for the interpretation of optical absorption experiments^{8,10} from which it was concluded that in *N*-phenylpiperidone derivative **1** (R = H) the population of the axial conformation is ca. 49% at 183 K. An enthalpy difference was estimated of $\Delta H^0 \approx 0.7$ kcal/mol in favor of the axial form. The phenyl group is expected to have a clear steric preference for the equatorial orientation, probably similar

to that in cyclohexane ($\Delta G = 2.7$ kcal/mol at 973–1073 K),³⁶ but at least 1.7 kcal/mol according to NMR studies.¹⁰ Thus, the experiment indicates that TBI between the aniline donor and the dicyanomethylene acceptor in **1** stabilizes the axial conformation by at least $1.7 + 0.7 = 2.4$ kcal/mol. It is gratifying that we do find a clear stabilization in the MP2 calculation with the closest related model system **11**, but the calculated value of 1.12 kcal/mol (Table 7) is clearly too small. Several explanations come to mind. In the first place, the *N*-phenyl donor has a lower ionization potential than the *N*-methyl group, thus TBI can be expected to be stronger. In the case of **5** vs **11** the difference in ionization potential (IP) is $8.70 - 8.37 = 0.33$ eV,¹⁷ and the increase in stabilization of the axial form is 1 kcal/mol (cf. Table 7). The IP of *N*-phenylpiperidine is only 7.72 eV,³⁷ so there may well be a significant further differential stabilization. On the other hand, a delocalization of the HOMO on the aromatic ring would disfavor TBI. Second, our calculations have pointed to the importance of electron correlation. More extensive investigations of this aspect, including other approaches to obtain the correlation energy, are clearly extremely desirable. Another relevant factor may be the effect of the medium on molecular properties: the dipole repulsion effect which disfavors the axial conformation (section 4.3) is likely to be smaller in solution. Finally, the magnitude of the stabilizing effect of TBI can only be properly evaluated on the basis of a reference point, viz. the axial/equatorial energy difference in *N*-phenylpiperidine, for which reliable experimental data are lacking. A potential problem when comparing theory and experiments is the role of entropy: $T\Delta S$ can easily be ca. 1 kcal/mol under normal experimental conditions,³⁸ but accurate evaluations of entropic effects are hard to make. For the series of compounds **1**, ΔS° values of 3 to 6 cal/mol K were estimated, the entropy being lower in the axial conformer.¹⁰

Given the fact that TBI is quite effective in the N inversion TS, one might wonder whether a distinction between axial and equatorial forms in *N*-phenylpiperidone donor–acceptor systems is still meaningful. It is conceivable that the planar trigonal geometry around nitrogen corresponds to an energy minimum. The X-ray data on an extensive series of compounds **1** and related tropane derivatives,^{9,10} however, show clearly pyramidal nitrogens in axially and equatorially substituted systems.

4.5. Geometric Features. In the model originally proposed by Hoffmann et al.^{1,2} to account for TBI over three σ bonds, the σ and σ^* MOs of the central bond play a dominant role. They mediate the interaction between the functional groups by mixing with their basis orbitals. If this involves mixing of σ^* with an occupied combination of functional group orbitals, weakening and thus elongation of the central C–C bond can result. The validity of this simple model, and especially the importance of the σ^* orbitals, has been questioned,³⁹ and other descriptions of TBI have been presented.^{5,40,41} From experimental X-ray diffraction studies^{9,10} it has been concluded that

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lengthening of the central bonds in piperidone and tropanone derivatives can amount to ca. 0.02 Å. In Tables 2, 4, and 5, relevant information on the optimized structures is given. In all conformations, the length of the C₂–C₃ bond increases with increasing acceptor strength. In the equatorial conformations of the piperidines, this bond is consistently shorter than that in the cyclohexane reference compounds 14–17, but the effects of changing the acceptor group are virtually identical in the two series. Thus there is no noticeable geometric effect of TBI in the equatorial conformation. In the axial and TS forms, the C–C bond is always longer than that in the equatorial conformation. Here however we can see a clear trend: stronger TBI goes together with an elongation of the C–C bond. This holds when the series with different acceptors is compared but also when TBI is increased by replacing *N*-H with *N*-methyl. The effect of the orientation of the nitrogen lone pair, and thus of TBI, on the length of the central C–C bonds is further illustrated in Figure 9. The differences between different computational methods are analogous to those described above for the energetic effects: the largest TBI effect on the bond lengths is found when the geometries are optimized with electron correlation, HF/3-21G is more sensitive to TBI than HF/6-31G*, and only minor TBI effects are found in the AM1 results.

As discussed above, the carbenium ions 18, 7, and 13 have somewhat unusual structures. The two conformations of 18 do not differ much in energy, although at the correlated level the "puckered" form is favored by 4.6 kcal/mol. When through-bond donor–acceptor interaction enters into play, the puckered conformations 7b and 13b are strongly favored. In this conformation the acceptor has a strong hyperconjugative interaction with the C₂–C₃ and C₅–C₆ bonds, which now further interact with the electron donor group. As a result of this, the C–C bonds become extremely weak and long. At the HF/3-21G level spontaneous Grob fragmentation results when the symmetry is lowered along the *a*" mode with a negative force constant. Given the importance of electron correlation, it is expected that the same will happen at the MP2/6-31G* level.

The experimental estimate of the bond lengthening due to TBI in piperidone and tropanone derivatives with the dicyanomethylene acceptor is ca. 0.01–0.02 Å. Our calculated values for 5 and 11 at the HF/3-21G level are 0.014 and 0.017 Å, respectively. Considering that electron correlation should further increase the effect, we conclude that theory is in principle able to achieve a good agreement with experiment for this structural manifestation of TBI.

On theoretical grounds TBI in the piperidyl carbenium ion 7 was predicted³ to be accompanied by a pyramidalization of the acceptor carbon atom with a positive value of θ , i.e. the hydrogen at C-4 is displaced toward the axial side. Our calculations show that such a pyramidalization also occurs in the cyclohexyl carbenium ion 18b, so TBI of a donor–acceptor type is not a prerequisite for this pyramidalization. However, in the donor–acceptor systems TBI does lead to a positive contribution to the pyramidalization. In the equatorial conformers the values of θ are essentially the same as in the reference compounds, but in the TS in the *N*-H series and in the axial conformations they are greater. The "sensitivity" to TBI is as before: MP2/6-31G* > HF/3-21G > HF/6-31G* > AM1. According to experimental X-ray data,^{9,10} the pyramidalization angle θ varies between -2° and $+3^\circ$ in dicyanomethylene derivatives of *N*-phenylpiperidones

when the substituent on N is equatorial. In axially substituted derivatives the pyramidalization is positive, and can be as large as 8° . Although the trend in the computed values conforms to expectation, the magnitude of this pyramidalization is underestimated. The results for 6 and 7 suggest that electron correlation may be particularly important for a proper description of this aspect of the structure.

The pyramidalization angle α of the donor group reflects the change of the shape of the potential energy surface along the inversion coordinate. Lowering of the barrier goes with a shift of the minima in the direction of the planar geometry.

5. Conclusions

The results discussed above indicate that the geometric and energetic effects of through-bond donor–acceptor interactions are not easily reproduced by quantum-chemical calculations. The Hartree–Fock ab initio results are strongly basis set dependent. Moreover, electron correlation is shown to be essential, especially because its effects appear to be more important as TBI is stronger. The HF calculations with the 3-21G and 6-31G* basis sets give qualitatively similar results, but all effects of donor–acceptor interaction are much more pronounced in the 3-21G calculations. Thus, as far as a qualitative comparison of geometry-dependent D–A interaction effects is concerned, HF/3-21G calculations appear to be a useful starting point. The energy differences are of the same order as those obtained with MP2. However, the geometric details that emerge at the 3-21G level are probably not very reliable. Semiempirical AM1 calculations are not very useful at all for the study of TBI.

Our calculations confirm that TBI is extremely strong in the piperidyl carbenium ions 7 and 13, leading to structures with C–C bond lengths of >1.7 Å, which undergo spontaneous Grob fragmentation upon breaking of the imposed C_s symmetry. This result implies that in the actual heterolytic fragmentation process the breaking of the bond to the leaving group may well occur in concert with the fragmentation.

From a comparison of the present results with experimental data, we conclude that for quantitatively correct results MP2/6-31G* geometry optimizations constitute the minimum level of theory that may be adequate. Unfortunately these calculations are still not practical for molecules as large as 1, for which the actual experimental data are available. The recent development of density functional theory (DFT) for molecular calculations opens a perspective for an economical way to include correlation effects. Studies aimed at evaluating the usefulness of the different variants of DFT in the field of TBI are planned for the near future.

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