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Intramolecular hydrogen bond in the push–pull CF_3-aminoenones: DFT and FTIR study, NBO analysis

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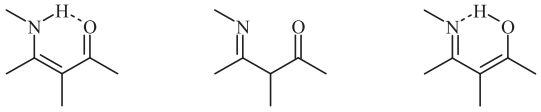
ABSTRACT

Postulated conformers of trifluoromethylated β-aminoenones stabilized by intramolecular NH···O and N···HO bonds were studied by IR and NMR spectroscopy and evaluated with quantum chemical calculations (B3LYP/6-311+G(d,p), MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) and MP2/6-31G(d,p)) and NBO analysis. The influence of the nature of EWG, substituents at the nitrogen atom and double bond, and of orbital interactions of heteroatoms and double bonds in these structures on the proton affinity of basic and acid centers, strength of hydrogen bonds, and the energy of tautomeric transfers is discussed. The theoretical results agree satisfactorily with the experimental observations.

1. Introduction

Trifluoromethylated β-aminoenones belong to the class of push–pull alkenes, i.e., systems bearing electron donating (EDG) and electron withdrawing (EWG) groups at the vicinal sp^2-carbon atoms. Such compounds are very useful building blocks and widely used for the synthesis of analogs of natural substances[1,2] and the assembly of various fluorinated heterocycles.[3–8] Moreover, push–pull aminoenones are also of considerable interest from a theoretical point of view because they can exist in several stereoisomeric and tautomeric forms, especially for derivatives bearing at least one hydrogen on the nitrogen atom. In the last case the intramolecular hydrogen bond often determines the preferable configuration of the molecule. Because the reactivity of push–pull systems depends strongly on their structure and, particularly, geometry,[9] it is important to understand the influence of the nature of both EWG and EDG as well as the olefin substituent on the electron distribution and the stereochemistry of these compounds.

The role of the hydrogen bond in the existence of different conformers and tautomers of push–pull aminoenones, as well as their equilibrium, which depends on the nature of substituents, crystal structure and experimental conditions, such as temperature and solvent polarity has been intensively studied for last decade by NMR and IR spectroscopy, X-ray diffraction and, finally, quantum chemistry.[10,11] In general, the following tautomeric forms of β-aminoenones could be presented: aminoketone **A**, iminoketone **B** and iminoenol **C** (Chart 1).



A B C

Chart 1. Possible tautomeric forms of β-aminoenones.

It has been previously shown that intramolecular hydrogen bonding helps to stabilize some tautomers of substituted β-aminoenones and related compounds.[12–18] It is well known that N···O plays a determinant role in protein folding and DNA pairing.[10] The compounds bearing such bonding are more stable than isostructural systems having hydrogen bond N···HO in spite of the fact that the latter is generally stronger. However, it was found that 1,3-enaminoketonatoboron difluorides in solution exist as a 1:1 mixture of **A** and **C** tautomers, but in the solid state the amount of the latter form increases.[19] Similarly, two tautomeric forms of phosphorus bearing aminoenones were registered in the solid state.[20] It was reported that some tautomers self-associate into dimers with the different type of H-bonds.[21,22] Non-polar aprotic solvents favor the imino-enol form **C** of the azomethyne derivatives obtained from substituted *ortho*-hydroxy aromatic aldehydes, while the use of

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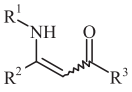
polar solvents shifts the equilibrium toward the tautomer **A**.[11] The barrier to such isomerization for these compounds is lowered with increase of the solvent polarity and its proton acceptor ability.[23] For example, low-barrier O···H···N imine-oxo tautomeric form is characteristic for such type compounds in acetonitrile due to solvent/proton interaction.[24] It has been recently reported that H-bond donors lower the energy of the proton-transfer transition state up to barrier-free tautomeric transformation.[23,25] According to quantum chemistry calculations and X-ray analysis, (*Z*)-4,4,4-trifluoro-3-(2-hydroxyethylamino)-1-(2-hydroxyphenyl)-2-buten-1-one forms three tautomeric forms bearing intramolecular hydrogen bonds OH···O and NH···O.[26] Interestingly, the most stable tautomer is one having the oxygen atom of the carbonyl moiety participate in the formation of both these bonds while intermolecular bonds OH···O form a polymeric structure. Functional groups bearing a mobile proton can also take part in H-bonding. Thus, intermolecular bond =C–H···O participates in CF_3-aminoenones self-association in both non-polar solvents and solid state.[27] This is the first example of a strong hydrogen bonding formed by an olefinic proton. Usually, the conformation analysis was carried out for push–pull systems with general formula Me_2N–CH=CH–C(O)R, where R=Me, CF_3.[28–32] The following factors were taken into account: basicity of nitrogen and oxygen atoms in different conformers, the impact of environment polarity on molecule structure and its interaction with proton- and electron-donating solvents, formation of dimers with bonds C–H_α···O=C and C–H_α···F–C. The study of conformational behavior of CF_3-aminoenone bearing secondary amino group (NHMe) has shown that the solvents having proton withdrawing groups (such as P=O, S=O, etc.) destroy intramolecular bond NH···O in the *Z*,*Z*-isomer due to formation of intermolecular H-bonds, which favor the *E*,*E*-configuration.[33] Finally, it has been found that in contrast to α-unsubstituted trifluoromethylated β-aminoenones their α-bromo substituted analogs have unusual configuration due to the stabilizing effect of a weak NH···Br bond.[34] Here, we describe the dependence of the strength of intramolecular hydrogen bond in push–pull CF_3-aminoenones on the nature of the nitrogen and olefin substituent and its role in the tautomeric equilibrium. The research was carried out by IR and NMR spectroscopy and quantum chemistry calculations for the enones **1**–**10** (Chart 2). In spite of the fact that two geometric isomers are possible for each tautomeric form of aminoenones, we have studied *Z*-isomers because they are stabilized by hydrogen bond and therefore are more favored. The calculations are done with the B3LYP/6-311+G(d,p), MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p), and MP2/6-31G(d,p) levels of theory and NBO analysis for aminoenone conformers **A** with *syn*- and *anti*-planar arrangement of C_α=C_β and C=O bonds as well as for *syn*- and *anti*-conformers of their imino-enol tautomeric form **C** (Chart 3).



compound	R^1	R^2	R^3
1	Me	Ph	CF_3
2	Me	Ph	Me
3	Ph	Me	CF_3
4	Ph	Me	Me
5	2-$H_2NC_6H_4$	Me	CF_3
6	2-$H_2NC_6H_4$	Me	Me
7	Me	Me	CF_3
8	Me	Me	Me
9	*i*-Pr	Ph	CF_3
10	2-$H_2NC_6H_4$	Hex	CF_3

Chart 2. The studied β-aminoenones.

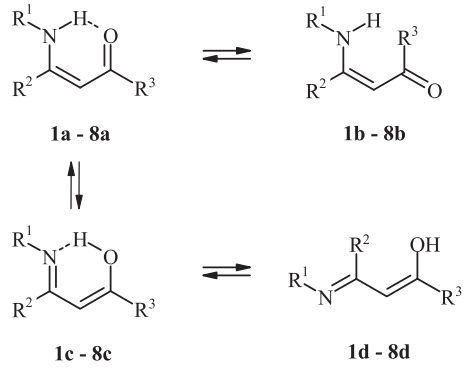


Chart 3. The equilibria for β-aminoenones bearing secondary amino group.

2. Results and discussion

2.1. Synthesis of aminoenones 9–11

The reaction of ynones **12a**,**b** with 1 equiv of primary (isopropylamine) or secondary (pyrrolidine) amines as well as diamine bearing primary amino groups (*o*-phenylenediamine) under very mild conditions (room temperature, benzene or acetonitrile, 3–24 h) affords the corresponding aminoenones **9**–**11** in high yields (Chart 4).

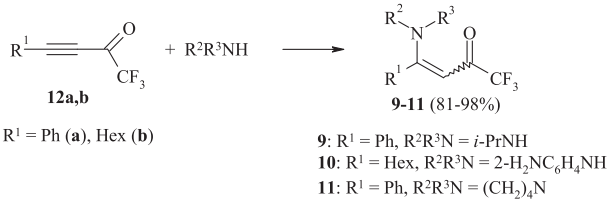


Chart 4. The synthesis of β-aminoenones **9**–**11**.

According to NMR spectroscopy, these enones were isolated as a single geometric isomer. Their configuration was assigned on the basis of ^{1}H–^{1}H 2D homonuclear NOESY experiment (Chart 5). For example, in the spectrum of enone **9** there is one NOE peak between the resonance of the olefinic proton and the *ortho*-protons of the aromatic ring. At the same time no correlation has been observed between the protons of CH= and isopropylamino groups. Similarly, the olefinic proton of aminoenone **10** has only one cross peak with the α-methylene protons of the hexyl moiety. Similarly, in the NOESY spectrum of enone **10** only one cross peak between olefinic and α-methylene protons is observed. Moreover, in both

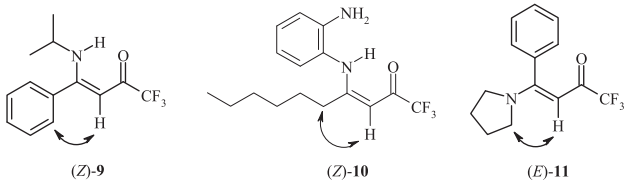


Chart 5. Main NOESY correlations for aminoenones **9**–**11**.

cases the peak of the amino proton is shifted (δ=11–12 ppm in $CDCl_3$) due to the formation of the hydrogen bond between C=O and NH. For the latter compound **10** the protons of the primary amino group resonate at ~3.8 ppm. These data undoubtedly confirm the (*Z*)-configuration of aminoenones **9** and **10**. In contrast, aminoenone **11** bearing a tertiary amino group has the (*E*)-configuration: the olefinic proton has a cross peak only with the methylene protons of pyrrolidine moiety in the NOE spectra.

The additional confirmation of this assignment has been obtained by the analysis of their IR spectra: the ratio of intensities observed for the C=O (1608–1657 cm^{-1}) and C=C (1530–1585 cm^{-1}) stretching vibration bands strongly suggests a *s-cis*-conformation of the C=C–C=O moiety.[35,36]

The push–pull aminoenones bearing a trifluoromethyl group have a very polar double bond. It is well known that the ^{13}C chemical shifts difference between adjacent olefinic carbon atoms can serve as reliable parameter of double bond polarization.[37] These values achieve 79.7, 85.7, and 78.1 ppm for aminoenones **9**, **10**, and **11**, respectively, and are much higher than for non-fluorinated analogs (~55–65 ppm).[38] In contrast to non-fluorinated aminoenones[39] their trifluoromethylated analogs as classical push–pull systems have a low-barrier to rotation about the carbon–carbon double bond and therefore can readily undergo the *Z*,*E*-isomerization.[40] Taking into account this fact we assume that the stereoselective formation of aminoenones **9**–**11** proceeds by the same pathway but further isomerization occurs leading to a more stable isomer. The similar *E*,*Z*-isomerization for polar acrylic systems, such as enammonium salts of captodative formyl- and carbonyl(amino)alkenes and their derivatives was reported.[41–44]

Interestingly, the aminoenone **10** undergoes further transformations after standing in $CDCl_3$ solution at room temperature for a week. Careful analysis of the ^1H and ^{13}C NMR spectra allows us to conclude that a new compound has the structure of 1,4-diazepine **13** (Chart 6).

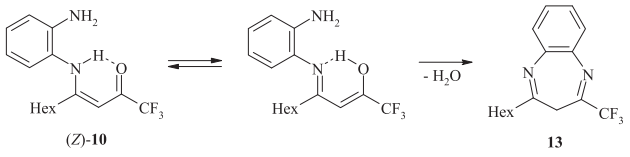


Chart 6. Cyclization of aminoenone **10**.

This heterocycle was obtained by a separate experiment from ynone **12b** and *o*-phenylenediamine in acetonitrile with good yield. This result allowed us to suggest a hypothesis that both formation of heterocycle **13** and enamino-ketone–imino-enol tautomerization of push–pull aminoenones bearing electron withdrawing substituents at both amino and carbonyl functional groups pass through the same transition state.

2.2. Theoretical calculations: energies, geometry, proton affinities

The theoretical analysis was performed for compounds **1**–**8** bearing substituents at both nitrogen and olefinic carbon atoms, which have different electronic and steric parameters. *syn*-Conformers of both tautomeric forms **A** and **C** are stabilized by intramolecular hydrogen bonds N–H···O or N···H–O, respectively. The calculations, which were performed at the B3LYP/6-311+G(d,p) and MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) level of theory indicate that formation energy for *syn*-conformers of aminoenones **1a**–**6a** and **8a** is lower for 9–11 kcal/mol than its *anti*-conformers **1b**–**6b** and **8b** regardless of the nature of EWG or a substituent at the olefinic carbon atom (Table 1).

Table 1
Total (E_t) and relative (ΔE) *syn*- and *anti*-conformers of enamino-ketones **1a**,**b**–**8a**,**b** energy

Entry	Molecule	B3LYP/6-311+G**		MP2/6-311+G**//B3LYP/6-311+G**	
		$-E_t$ (ZPE)[a], a.u.	$-\Delta E$ (ZPE)[a], kcal/mol	$-E_t$, a.u.	$-\Delta E$, kcal/mol
1	**1a**	854.751739	0	852.7350365	0
2	**1b**	854.734654	10.70	852.7196861	9.84
3	**2a**	556.913525	0	555.482248	0
4	**2b**	556.896534	10.66	555.468223	8.80
5	**3a**	854.756908	0	852.736633	0
6	**3b**	854.739082	11.19	852.720254	10.28
7	**4a**	556.919402	0	555.484220	0
8	**4b**	556.901725	11.09	555.468589	9.81
9	**5a**	910.118004	0	907.970949	0
10	**5b**	910.100424	11.03	907.954567	10.28
11	**6a**	612.280282	0	610.718840	0
12	**6b**	612.262901	10.91	610.703737	9.48
13	**7a**	663.025978	0	661.518739	0
14	**7b**	663.014872	6.97	661.506044	7.97
15	**8a**	365.187395	0	364.265311	0
16	**8b**	365.169434	11.27	364.249590	9.86

[a] Calculations corrected by zero-point energy.

As for enone **7**, its *syn*-conformer **7a** stability is 2–4 kcal/mol lower than for its non-fluorinated analog **8a**. The ΔE values between *syn*- and *anti*-conformers for the imino-enol form increase by 1.5–2 times for compounds bearing either aryl (**1**, **2**) or methyl (**7**, **8**) substituents at the β-carbon atom (Table 2). *syn*-Conformers **1c** and **7c** are more stable by 2–3 kcal/mol due to the electron withdrawing effect of the CF_3-group. The aryl moiety at nitrogen atom (for imino-enols **3**–**6**) provides the same electronic effect that results in ΔE decreasing. At the same time *syn*-conformers of tautomeric forms of non-fluorinated enones **4c** and **6c** proved to be insignificantly more stable than their CF_3-bearing analogs **3c** and **5c**. The study of the dependence of ΔE on substituent nature in both tautomeric forms is possible with the estimation of factors that contribute to *syn*-conformers stabilization, such as intramolecular bond strength and degree of electron density delocalization in the formed cyclic systems.

Table 2
Total (E_t) and relative (ΔE) *syn*- and *anti*-conformers of imino-enols **1c**,**d**–**8c**,**d** energy

Entry	Molecule	B3LYP/6-311+G**		MP2/6-311+G**//B3LYP/6-311+G**	
		$-E_t$ (ZPE)[a], a.u.	$-\Delta E$ (ZPE)[a], kcal/mol	$-E_t$, a.u.	$-\Delta E$, kcal/mol
1	**1c**	854.738507	0	852.725659	0
2	**1d**	854.711078	17.21	852.698811	16.85
3	**2c**	556.902870	0	555.475208	0
4	**2d**	556.879631	14.58	555.451510	14.87
5	**3c**	854.746715	0	852.731328	0
6	**3d**	854.727698	11.93	852.711310	12.56
7	**4c**	556.912148	0	555.481427	0
8	**4d**	556.892058	12.60	555.460654	13.03
9	**5c**	910.107748	0	907.966335	0
10	**5d**	910.090351	10.92	907.946976	12.15
11	**6c**	612.273218	0	610.716883	0
12	**6d**	612.252666	12.90	610.695618	13.34
13	**7c**	663.012464	0	661.509079	0
14	**7d**	662.983591	18.12	661.480500	17.93
15	**8c**	365.176689	0	364.258137	0
16	**8d**	365.152794	14.99	364.233407	15.52

[a] Calculations corrected by zero-point energy.

Calculated values of the intramolecular hydrogen bond N–H···O length and the frequency shifts $\Delta\nu$(N–H) for *syn*-conformers (**1a**–**8a**) versus their *anti*-conformers (**1b**–**8b**) change symbatically and therefore can serve as a bond strength measure (Table 3).

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Table 3
Bond distance N–H···O ($d_{H\cdots O}$), frequency shift $\Delta\nu$(N–H) and second-order perturbation energy $E^{(2)}$ for orbital interactions in *syn*-conformers of enamino-ketones **1a**–**8a**[a]

Entry	Molecule	$d_{H\cdots O}$, Å	$\Delta\nu$ (N–H), cm^{-1}	$E^{(2)}$, kcal/mol			
				$n_O \rightarrow \sigma^*_{N-H}$	$n_N \rightarrow \pi^*_{C\alpha=C\beta}$	$n_N \rightarrow \pi^*_{C=C(Ar)}$	$\pi_{C\alpha=C\beta} \rightarrow \pi^*_{C=O}$
1	**1a**	1.844	249	12.48	65.37		38.42
2	**2a**	1.813	301	14.66	61.93		32.26
3	**3a**	1.808	314	14.77	61.74	18.51	38.17
4	**4a**	1.773	393	17.67	57.49	23.89	31.73
5	**5a**	1.835	290	13.11	62.07	5.61	38.52
6	**6a**	1.802	339	15.52	58.35	6.11	32.15
7	**7a**	1.844	237	12.51	66.72		38.90
8	**8a**	1.835	287	13.38	63.04		32.11

[a] Calculated using B3LYP/6-311+G**.

When the CF_3 group is replaced with methyl, the H-bond length decreases for 0.01–0.03 Å. As expected the presence of substituents of the same type in enones **3a**–**6a** results in formation of shorter H-bonds due to the electron withdrawing effect of the aryl substituent at nitrogen that increases N–H group acidity. The shortest H-bond corresponds to the highest value of $\Delta\nu$(N–H) for these conformers.

In contrast to aminoenones, imino-enols bearing a CF_3-group have a shorter intramolecular bond O–H···N than their methyl-bearing analogs (Table 4). It is not surprising that this bond length increases up to 1.630–1.654 Å when the *N*-methyl moiety is replaced with *N*-phenyl. Low-frequency shift ν(O–H) in imino-enols significantly exceeds shift ν(N–H) in aminoenones and corresponds to formation of a stronger H-bond. The greatest shift $\Delta\nu$(O–H) (1310 cm^{-1}) is observed in conformer **7c**, which has the shortest H-bond (1.568 Å).

In enamino-ketones bearing aryl (**1a**, **2a**) or methyl (**7a**, **8a**) as the olefinic substituent the PA value for the deprotonated nitrogen atom is higher than for the protonated oxygen atom for 132–139 kcal/mol. According to Hammond's postulate, the decrease of ΔPA for acidic and basic centers favors tautomeric transition.[45,46] The value of ΔPA for aminoenones **3a**–**6a** lowers up to 122–126 kcal/mol because of reduction of nitrogen atom PA with the length of H-bond decrease and corresponds to a lower TS energy. Interestingly, the introduction of more electron withdrawing CF_3 instead of the methyl one into tautomeric form **A** decreases the PA of both heteroatoms in equal extent. As a result, the value of ΔPA is not changed. Similar relations are observed for imino-enols **C**. However, despite the shortest H-bond in trifluoromethylated conformer **7c**, ΔPA values for its nitrogen and oxygen atoms as well as in methyl substituted conformer **8c** are the highest (134.05 and

Table 4
Bond distance N–H···O ($d_{H\cdots N}$), frequency shift $\Delta\nu$(O–H) and second-order perturbation energy $E^{(2)}$ for orbital interactions in *syn*-conformers of imino-enols **1c**–**8c**[a]

Entry	Molecule	$d_{H\cdots N}$, Å	$\Delta\nu$(OH), cm^{-1}	$E^{(2)}$, kcal/mol			
				$n_N \rightarrow \sigma^*_{O-H}$	$n_O \rightarrow \pi^*_{C\alpha=C\beta}$	$n_N \rightarrow \pi^*_{C=C(Ar)}$	$\pi_{C\alpha=C\beta} \rightarrow \pi^*_{C=N}$
1	**1c**	1.578	1236	—[b]	54.38		20.83
2	**2c**	1.611	1141	41.21	53.78		25.45
3	**3c**	1.630	1043	37.53	53.99	10.52	20.74
4	**4c**	1.643	962	35.41	53.74	11.46	25.60
5	**5c**	1.637	1032	36.74	52.37	8.34	20.60
6	**6c**	1.654	977	33.99	52.36	10.31	25.67
7	**7c**	1.568	1310	48.68	55.52		21.85
8	**8c**	1.595	1202	43.36	54.64		26.48

[a] Calculated using B3LYP/6-311+G**.
[b] High polarization of O–H bond.

Enamino-ketone tautomeric form **1a**–**8a** is more stable by 4.4–8.5 kcal/mol (according to B3LYP/6-311+G(d,p)) and by 1.2–6.5 kcal/mol (according to MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p) and MP2/6-31G(d,p)) (Table 5). In the case of trifluoromethylated aminoenones this difference is higher. At the same time it is lower for molecules **3** and **5**, which contain a phenyl substituent at nitrogen atom and increases a tautomeric transition probability. Transition state (TS) energy ($\Delta G^{\#}$) for trifluoromethylated molecules is higher than for non-fluorinated ones but decreases for compounds **3** and **5** and therefore corresponds to a lesser distance for N···H and to a greater distance for O···H in transition state. Both $\Delta G^{\#}$ and ΔE parameters decrease with the replacement of the CF_3-substituent with methyl and are the lowest for compound **4** (2.33 kcal/mol). The length of the H-bond in its enamino-ketone **4a** form is the least and serves as a criterion for the easiest tautomeric transformation **A**→**C**.[10]

Proton affinity (PA) of oxygen and nitrogen atoms in *syn*-conformers of both tautomers defines the strength of intramolecular hydrogen bonds and capacity of molecules for tautomeric transformation (Table 6).

Table 5
Relative total energy ΔE (kcal/mol) for tautomers **1a**–**8a** and **1c**–**8c**, free energy for tautomeric transition $\Delta G^{\#}$ (kcal/mol) and bond distance $d_{N\cdots H}$ and $d_{O\cdots H}$ in transition states (TS)

Entry	Molecule	$-\Delta E$ (ZPE)[a]	$-\Delta E$[b]	$-\Delta E$[c]	TS[c]		
					d(N···H), Å	d(O···H), Å	$\Delta G^{\#}$
1	**1**	8.30	6.09	6.28	1.311	1.160	7.18
2	**2**	6.69	4.42	5.14	—[d]	—[d]	—[d]
3	**3**	6.40	3.33	4.11	1.281	1.184	5.73
4	**4**	4.55	1.75	3.02	1.261	1.200	2.33
5	**5**	6.44	2.90	3.52	1.279	1.184	5.01
6	**6**	4.43	1.23	2.29	1.256	1.203	4.58
7	**7**	8.48	6.06	6.50	1.312	1.157	7.29
8	**8**	6.72	4.50	5.30	1.285	1.177	6.74

[a] Calculated using B3LYP/6-311+G**, ΔE corrected by zero-point energy.
[b] Calculated using MP2/6-311+G**//B3LYP/6-311+G**.
[c] Calculated using MP2/6-31G**.
[d] Tautomer **2a** is formed.

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Table 6
Total energy (E_t) for *syn*-conformers of enamino-ketones **1a**–**8a** and imino-enols **1c**–**8c**, proton affinity (PA)[a] of corresponding nitrogen and oxygen

Entry	Molecule	$-E_t$ (ZPE)[b] a.u.	PA kcal/mol	ΔPA[c]	Molecule	$-E_t$ (ZPE)[b] a.u.	PA kcal/mol	ΔPA[d]
1	**1a**, N^-	854.198303	347.28	131.93	**1c**, O^-	854.198302	338.98	125.20
2	**1a**, OH^+	855.094920	215.35		**1c**, NH^+	855.079188	213.78	
3	**2a**, N^-	556.337841	361.24	132.85	**2c**, O^-	556.337841	354.56	128.36
4	**2a**, OH^+	557.277492	228.39		**2c**, NH^+	557.263357	226.20	
5	**3a**, N^-	854.215882	339.49	126.14	**3c**, O^-	854.215882	333.10	124.07
6	**3a**, OH^+	855.096914	213.35		**3c**, NH^+	855.079825	209.03	
7	**4a**, N^-	556.357400	352.66	126.15	**4c**, O^-	556.357384	348.11	126.58
8	**4a**, OH^+	557.280367	226.51		**4c**, NH^+	557.265181	221.53	
9	**5a**, N^-	909.580203	337.47	122.37	**5c**, O^-	909.580203	331.03	121.66
10	**5a**, OH^+	910.460788	215.10		**5c**, NH^+	910.441404	209.37	
11	**6a**, N^-	611.722004	350.32	122.76	**6c**, O^-	611.722004	345.89	124.32
12	**6a**, OH^+	612.642926	227.56		**6c**, NH^+	612.626310	221.57	
13	**7a**, N^-	662.466999	350.76	139.20	**7c**, O^-	662.466999	342.28	134.05
14	**7a**, OH^+	663.363118	211.56		**7c**, NH^+	663.344297	208.23	
15	**8a**, N^-	364.604771	365.60	139.27	**8c**, O^-	364.604771	358.88	136.43
16	**8a**, OH^+	365.548077	226.33		**8c**, NH^+	365.531188	222.45	

[a] Calculated using B3LYP/6-311+G** as energy of protonation and deprotonation of molecules.
[b] Total energy corrected by zero-point energy.
[c] ΔPA=PA(**1a**–**8a**), N^-–PA(**1a**–**8a**), OH^+.
[d] ΔPA=PA(**1c**–**8c**), O^-–PA(**1c**–**8c**), NH^+.

136.43 kcal/mol). They correspond to the highest TS energy values (Table 5). The lowest ΔPA value (121.66 kcal/mol) refers to conformer **5c** having the most acidic O–H and basic C=N moieties.

2.3. NBO Analysis

Donor–acceptor interactions of lone electronic pairs (LEP) of heteroatoms and double bonds in the studied molecules were estimated with the NBO method within the limits of second-order perturbation theory. The energy of electron delocalization $E^{(2)}$ reflecting interactions between the oxygen LEP and antibonding σ*-orbital of bond N–H $n_O \rightarrow \sigma^*_{N-H}$ was evaluated (Tables 3 and 4). In fact, as evident from Table 3, for aminoenones **1a**–**8a** there is a close relationship between $E^{(2)}$ and the length H-bond values. The biggest values of the energy were obtained for aminoenones **4a** and **6a** (Table 3, entries 4, 6), which are stabilized by a strong hydrogen bond, while this parameter is the smallest for aminoenones **1a** and **7a** bearing the longest NH···O distance (Table 3, entry 1, 7). It appears that a high value of $E^{(2)}$ for aminoenone **4a** might be explained by the influence of the *N*-phenylamino moiety. Indeed, in this case the electron withdrawing effect of an aryl substituent is reflected in energy of the nitrogen LEP interaction with antibonding π*-orbital of benzene ring $n_N \rightarrow \pi^*_{C=C(Ar)}$. Its values are significantly higher for enones **3a** and **4a** (18.51 and 23.89 kcal/mol) than for their analogs **5a** and **6a** (5.61 and 6.11 kcal/mol) bearing substituent NH_2 in the benzene ring.

The presence of the CF_3-group weakens this interaction as well but to a less extent. Conjugation in cycles formed with H-bonds is characterized by an energy of interaction between the nitrogen LEP and antibonding π*-orbital of the ethylene double bond $n_N \rightarrow \pi^*_{C\alpha=C\beta}$ and an energy of interaction between the bonding π-orbital of double bond and the carbonyl group antibonding π*-orbital $\pi_{C\alpha=C\beta} \rightarrow \pi^*_{C=O}$. Higher energy values should correspond to simultaneous increase of oxygen atom basicity and nitrogen atom acidity and therefore to H-bond strength increase. However, despite the energy increase no changes in hydrogen bond strength is observed. It is due to oxygen atom PA reduction (s.o.) because of the electron withdrawing effect of the trifluoromethyl substituent. As a result, there is no any formation energy dependence of aminoenone *syn*-conformers (Δ*E*) on the substituent nature (Table 1). Symbate Δ*E* and H-bond strength change with the replacement of the methyl group with the CF_3-group in molecule **7a** only with the absence of phenyl substituent, which influences the electronic distribution in the cycle.

In the case of imino-enols **1c**–**8c** the value $E^{(2)}$ for the $n_N \rightarrow \sigma^*_{O-H}$ orbital interaction exceeds significantly the energy of $n_O \rightarrow \sigma^*_{N-H}$ interaction in enamino-ketones **1a**–**8a** (Table 4). As in the amino-ketone form it varies in accordance with H-bond length and its highest value (48.68 kcal/mol) corresponds to molecule **7c** having the shortest bond OH···N. Moreover, $E^{(2)}$ values increase if the hydroxyl proton becomes more acidic (in the case of CF_3-enones). On the contrary, the presence of the N–Ar moiety in molecules **3c**–**6c** results in a decreasing of stability of these conformers due to weakening of the H-bonds (Table 2). In this case, the energy of $n_N \rightarrow \pi^*_{C=C(Ar)}$ interaction (8–11 kcal/mol) is less dependent on the effect of the substituent in the benzene ring due to interaction energy decreasing for imino-enols **5c** and **6c** (up to 27.99 and 26.49 kcal/mol, respectively) in comparison with aminoenones **5a** and **6a** (32.03 and 30.62 kcal/mol, respectively). The higher stability of *syn*-conformers of imino-enols **1c** and **7c** (Table 2) bearing a trifluoromethyl substituent refers to the presence of strong H-bonds in these molecules. But in the case of the phenyl substituent on nitrogen, the less stability of conformers **3c** and **5c** in comparison with their methyl bearing analogs **4c** and **6c** (Table 2, entries 5, 7, 9, 11) does not correspond to the strength of the H-bonds. Therefore, the stabilization of conformers **4c** and **6c** is caused mainly by the interaction energy $\pi_{C\alpha=C\beta} \rightarrow \pi^*_{C=N}$, which is higher for the methyl substituent (Table 4).

2.4. FTIR spectra

Aminoenones **9** and **10** are analogs of model compounds **1** and **5** used in calculations where substituents *i*-Pr and Hex were replaced with a methyl group for simplicity. In the solid state (IR spectra data) and in $CDCl_3$ solution (NMR data) these compounds have an enamino-ketone structure. The stretching vibration bands ν(N–H) (3200–3250 cm^{-1}) of solid substances are weak and broad. In the spectra of their diluted solutions (CCl_4 or cyclohexane) these bands remain weak but have clear peaks (3205 (**9**) and 3184 cm^{-1} (**10**), respectively) and refer to N–H groups participating in forming strong intramolecular H-bonds. This type of hydrogen bond is discussed and explained by either resonance assistance[47] or delocalization of charges.[48] A lower frequency band ν(N–H) in spectrum of the compound **10** indicates a higher strength of its H-bond as compared with compound **9**. This result agrees with a calculated strength of hydrogen bond in model aminoenones **5a** and **1a** (Table 3).

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It is well known that the oxygen of the carbonyl group is the only protonation center in push–pull aminoenones.[32,49] Considering that the strength of the H-bond depends on the properties of the basic center, we estimated the relative basicity of compounds **9** and **10**. To this end phenol was used as standard proton donor in CCl_4 solutions.[50] The relative basicity was evaluated with the low-frequency shift $\Delta\nu$(O–H) of its associated hydroxyl group. The $\Delta\nu$(O–H) for compounds **9** (167 cm^{-1}) and **10** (190 cm^{-1}) showed that the latter has a stronger intramolecular H-bond. The second peak $\Delta\nu$(O–H) (260 cm^{-1}) in the case of **10** refers to the formation of a hydrogen bond between PhOH and free NH_2 group. It should be noted that when the proton donor was added, compounds **9** and **10** underwent easy tautomeric transformation into the imino-enol form.[23,25] The appearance of a shoulder at 3300–3320 cm^{-1} on the low-frequency wing of the ν(O–H) band can serve as a sign of such isomerization. Its value $\Delta\nu$(OH) (280–300 cm^{-1}) characterizes the interaction between phenol and the nitrogen atom of the C=N group of the corresponding imino-enols. The decrease in temperature of the solutions results in shoulder disappearance and the bands of H-complexes of phenol with more stable tautomer **A** are observed. The appearance of the second tautomer of **10** in the presence of the proton donor confirms our scheme on azepine formation through the same transition state as the tautomerization **A**→**C**.

3. Conclusion

The hydrogen bonding in the push–pull CF_3-aminoenones substituted by various electron donating/withdrawing groups at nitrogen and olefinic carbon atoms was successfully predicted by quantum chemical calculations using B3LYP/6-311+G(d,p), MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p), MP2/6-31G(d,p) levels of theory and NBO analysis. It was shown that *syn*-conformers of these compounds are more stable by 9–11 kcal/mol than *anti*-conformers regardless of the nature of the substituents at the nitrogen or double bond. In contrast, the energy of formation of *syn*-conformers of the imino-enol tautomeric form depends on the amino moiety and decreases if a ArNH group is present. In all cases the barrier of tautomeric equilibrium is higher for trifluoromethylated aminoenones as compared with non-fluorinated analogs due to the electron withdrawing properties of CF_3 group and decreases for *N*-aryl substituted derivatives. As a consequence, CF_3-aminoenones bearing EWG at nitrogen can undergo a very easy condensation leading to nitrogen heterocycles. The conformer stability is explained with the superposition of orbital interaction of the heteroatom lone-pairs and double bonds. The theoretical study of hydrogen bonding in push–pull CF_3-aminoenones showed a good agreement with experimental results.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 MHz spectrometer with solutions in $CDCl_3$. Chemical shifts (δ) in parts per million are reported with use of the residual chloroform (7.25 for ^1H and 77.20 for ^{13}C) as internal references. The coupling constants (J) are given in Hertz (Hz). The IR spectra of solid compounds were taken on an ATR/FTIR Varian 3100 spectrometer. The GC/MS analyses were performed with a Shimadzu GCMS-QP5050A instrument (EI, 70 eV). The spectra of the H-bonded complexes with phenol were registered on a FTIR Varian 3100 spectrometer in CCl_4 solution with concentration of phenol of 0.02 mol/l and concentration of the substrate of 0.1 mol/l. The silica gel used for flash chromatography was 230–400 mesh. All reagents were of reagent grade and were either used as such or distilled prior to use. All the solvents were dried by standard procedures and freshly distilled prior to use.

4.2. General procedure for preparation of aminoenones 9–11

A mixture of the appropriate enone **12** (1 mmol) and amine (1.0 mmol) in benzene (2 mL) was stirred at room temperature for 3 h. Volatiles were evaporated in vacuo, the residue was pure target adduct (**9** and **11**) or purified (in the case of **10**) by column chromatography [silica gel, ether/hexane (2:1)]. The following aminoenones were obtained by this method.

*4.2.1. (Z)-1,1,1-Trifluoro-4-isopropylamino-4-phenylbut-3-en-2-one **9**.* Light yellow solid (236 mg, 92% 254 mg, 81% yield): mp 33 °C; ^1H NMR ($CDCl_3$): 1.19, 1.21 (s, 6H, $2CH_3$); 3.60–3.78 (m, 1H, NCH); 5.31 (s, 1H, CH=); 7.22–7.50 (m, 5H, Ph); 11.11 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 23.9 ($(CH_3)_2$); 47.2 (NCH_2); 90.0 (CH=); 116.4 (q, J=292.6, CF_3); 127.1, 128.9, 130.4, 134.3 (Ph); 169.7 (NC=); 175.8 (q, J=32.6, C=O). ^{19}F NMR ($CDCl_3$): −76.7. ^{15}N NMR ($CDCl_3$): −235.7. IR (ν, cm^{-1}) ($CDCl_3$): 1142, 1195, 1216 (C–F), 1571, 1583, 1607 (C=C, Ph, C=O), 3205 (N–H). Calcd for $C_{13}H_{14}F_3NO$: C 60.70; H 5.49; N 5.44. Found: C 60.81; H 5.68; N 5.27. MS, m/z (%): 257 (48, M^+); 188 (100), 146 (70), 104 (73).

*4.2.2. (Z)-4-[(2-Aminophenyl)amino]-1,1,1-trifluorodec-3-en-2-one **10**.* Light yellow solid (254 mg, 81% yield): mp 73 °C; ^1H NMR ($CDCl_3$): 0.81 (t, J=7, 3H, CH_3); 1.05–1.25 (m, 6H, $(CH_2)_3$); 1.40–1.55 (m, 2H, CH_2); 2.25–2.35 (m, 2H, CH_2); 3.79 (br s, 2H, NH_2); 5.56 (s, 1H, CH=); 6.70–7.15 (m, 4H, C_6H_4); 12.07 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): 14.0 (CH_3); 22.4, 27.8, 28.9, 31.2, 32.4 (CH_2); 89.5 (CH=); 116.4 (q, J=288.4, CF_3); 116.3, 118.7, 128.0, 129.5 (CH_{Ar}); 122.4 (C–NH); 142.5 (C–NH_2); 175.1 (NC=); 177.0 (q, J=33.0, C=O). ^{19}F NMR ($CDCl_3$): −76.4. IR (KBr, ν, cm^{-1}): 1124, 1136, 1182 (C–F), 1587, 1609, 1629 (C=C, Ph, C=O), 3356, 3456 (N–H). Calcd for $C_{16}H_{21}F_3N_2O$: C 61.13; H 6.73; N 8.91. Found: C 60.82; H 6.89; N 8.73. MS, m/z (%): 239 (15, M^+-CF_3); 226 (100).

*4.2.3. (E)-1,1,1-Trifluoro4-phenyl-4-pyrrolidin-1-ylbut-3-en-2-one **11**.* Light yellow solid (259 mg, 96% yield): mp 52 °C; ^1H NMR ($CDCl_3$): 1.80–1.95 (m, 2H, CH_2); 2.05–2.15 (m, 2H, CH_2); 3.15–3.25 (m, 2H, NCH_2); 3.45–3.55 (m, 2H, NCH_2); 5.34 (s, 1H, CH=); 7.25–7.55 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): 24.7, 25.0 ($(CH_2)_2$); 49.1, 50.6 ($N(CH_2)_2$); 87.4 (CH=); 117.9 (q, J=293.0, CF_3); 126.5, 128.2, 128.7, 136.4 (Ph); 165.5 (N–C=); 173.9 (q, J=32.4, C=O). ^{19}F NMR ($CDCl_3$): −76.9. ^{15}N NMR ($CDCl_3$): −249.3. IR (KBr, ν, cm^{-1}): 1139, 1150, 1192 (C–F), 1530 (C=C), 1579 (Ph), 1657 (C=O). Calcd for $C_{14}H_{14}F_3NO$: C 62.45; H 5.24; N 5.20, F 21.17. Found: C 62.81; H 4.96; N 5.26, F 20.98. MS, m/z (%): 270 (48, M^++1); 200 (100).

*4.2.4. 2-Hexyl-4-trifluoromethyl-3H-benzo[b][1.4]-diazepine **13**.* Oil; ^1H NMR ($CDCl_3$): 0.90 (t, J=7.0, 3H, CH_3); 1.20–1.45 (m, 6H, CH_2); 1.70–1.80 (m, 2H, CH_2); 2.55–1.65 (m, 2H, CH_2); 2.96 (s, 2H, CH_2); 7.30–7.55 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): 14.2 (CH_3); 22.7, 26.2, 29.0, 31.7, 40.4, 35.7 (CH_2); 119.2 (q, J=276.8, CF_3); 125.6, 127.6, 128.3, 129.1, 137.2, 141.2 (C_6H_4); 144.3 (q, J=35.7, −C=N); 161.3 (−C=N). ^{19}F NMR ($CDCl_3$): −71.5. ^{15}N NMR ($CDCl_3$): −71.0, −56.4. IR (film, ν, cm^{-1}): 1116, 1130, 1143 (C–F), 1640 (C=N), 1598 (Ar). Calcd for $C_{16}H_{19}F_3N_2$: C 64.85; H 6.46; N 9.45. Found: C 64.71; H 6.11; N 9.04. MS, m/z (%): 296 (2, M^+), 239 (19), 226 (100).

4.3. Computational details

Calculations were performed by the B3LYP/6-311+G(d,p), MP2/6-311+G(d,p)//B3LYP/6-311+G(d,p), and MP2/6-31G(d,p) methods as implemented in the Gaussian03 program package.[51] All calculated structures correspond to minima on the potential energy

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surface (PES) as proved by positive eigenvalues of the corresponding Hessian matrices. The DFT energies were calculated with the ZPE correction. The NBO analysis[52,53] as implemented into the Gaussian03 package was performed using the 6-311+G** basis set on the previously DFT optimized structures. The search and localization of transition states were performed with the synchronous transit approach QST2.[54]

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.061.

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