Superelectrophilic Activation of 4-Heterocyclohexanones. Implications for Polymer Synthesis. A Theoretical Study

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The stability and the reactivity of mono- and diprotonated 4-heterocyclohexanones as well as cyclohexanone in triflic acid have been studied at the PBE0/aug-cc-pvtz//PBE0/6-31+G** level of theory. In all cases the first protonation is an exergonic process occurring at a carbonyl oxygen except for 4-piperidone where a nitrogen atom is protonated fist. Second protonation is only slightly endergonic for all studied molecules except for cyclohexanone where the second protonation is very unfavorable thermodynamically. According to calculations, diprotonated 4-heterocyclohexanones are much more active in the reactions of triflic acid mediated polyalkoxyalkylation with aromatic hydrocarbons compared to monoprotonated ones. The increase of the reactivity of diprotonated 4-heterocyclohexanones is due to inductive effect rather than through space electrostatic influence as follows from the electronic structure analysis of dications. Moreover, the second protonation reduces the possibility of an aldol condensation side reaction, reducing the enol electrophilicity rendering heterocyclohexanones as promising monomers for superacid mediated polyhydroxyalkylation.

Introduction

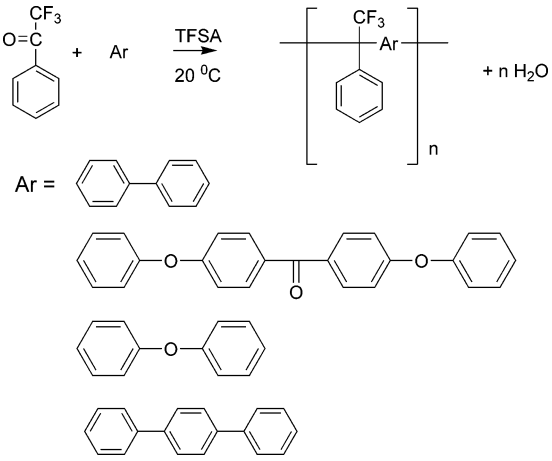
The superelectrophilic activation term was first introduced by Olah to explain the electrophile reactivities in superacids.[1] Superelectrophilic activation may take place when a cationic electrophile reacts with an acid to give a dicationic species. This type of activation has been suggested for the Friedel−Crafts-type reactions of 1,2-dicarbonyl groups,[2] aldehydes,[3] nitriles,[4] and other systems.[5]

Recently, it has been discovered that superacid catalyzed polyhydroxyalkylation reactions of aldehydes and ketones containing electron-withdrawing substituents with nonactivated aromatic hydrocarbons adjacent or relatively close to a carbocation center afford linear, high-molecular weight polymers (Scheme 1).[6,7]

It has been shown that the reactivity enhancement of carbonyl compounds bearing electron-withdrawing groups is due to stabilization of their lowest unoccupied molecular orbital (LUMO).[8]

In the case of triflic acid (TFSA) catalyzed polyhydroxyalkylation of aldehydes and ketones, the reactivity of diprotonated species is not sufficient to compensate for the large positive Gibbs energy of the second protonation; therefore, monocationic species are considered as active reaction intermediates.[9] On the other hand, the existence of diprotonated carbonyl molecules in superacids has been proven experimentally[10] when an alternative site for second protonation was available (heteroatom or electron-rich double bond). Thus, reports have been published regarding the studies of TFSA catalyzed condensation of 3-pyridinecarboxaldehyde with deactivated aromatic compounds and the observation of dication by low-temperature NMR.[11] The results provided a demonstration of the reactivity of dicationic electrophiles and suggested that protonation of a strong, adjacent base site can activate an electrophilic functional group, such as a carboxonium ion.

SCHEME 1: Scheme of TSFA Mediated Polycondensation of Carbonyl Compound with Aromatic Nucleophiles



A similar electrophile activation mechanism is presumably involved in the reaction of the diarylpiperidines synthesis (Scheme 1). They were prepared in good to excellent yields (80−99%) by the reaction of piperidones with benzene in the presence of TFSA. Under the same conditions cyclohexanone only produced a small amount of aldol condensation product.[12]

The authors suggested that the protonation of an amino group of **1b** activates carbonyl carbon, while in the case of cyclohexanone such activation is not possible. The activation observed in protonated **1b** is, thus, similar to that induced by electron-withdrawing substituents in carbonyl compounds,[8] and, therefore, piperidones could be considered as promising monomers for superacid mediated polymer synthesis. Moreover, a correlation has been observed between the heteroatom electronegativity

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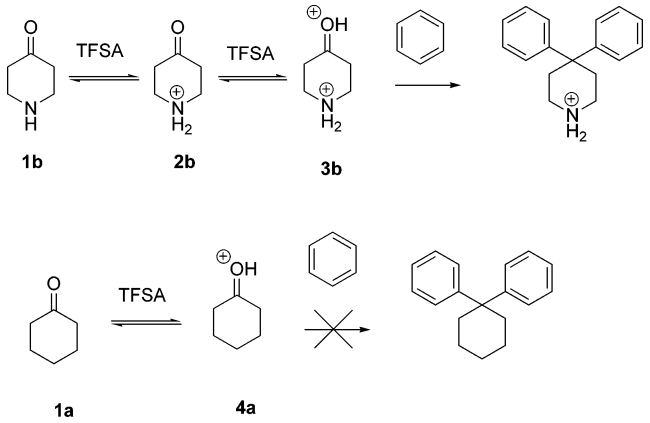
SCHEME 2: Reaction of 4-Piperidone (1b) and Cyclohexanone (1a) with Benzene in the Presence of TFSA



in 4-heterocyclohexanones[13] and the equilibrium constants for water and thiol addition reactions, reflecting activation of a carbonyl group. The aim of this paper is to explore the reactivity of diprotonated species of 4-heterocyclohexanones in TFSA and to obtain a deeper insight into the activation mechanism of carbonyl groups in the reactions of TFSA mediated polyhydroxyalkylation (Scheme 2).

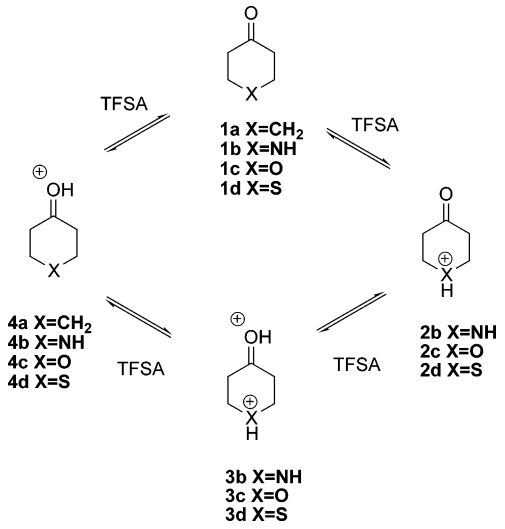
Computational Details

The prediction of the reliable reaction energies in solution where ionic species are involved is still a challenging task for modern computational chemistry. The model selection was based on its ability to reproduce experimentally determined pK_a's of different acids, since exact pK_a determination implies accurate calculation of the free Gibbs energies of solvated ionic species. The total free Gibbs solution energies of all molecules (G_s) were calculated as follows; $G_s = E_s + \Delta G_g$, where E_s is the total electronic energy in solution calculated at the PBE0/aug-cc-pvtz level using PBE0/6-31+G**[14] solution-phase optimized geometry and ΔG_g is the free Gibbs energy correction calculated as the difference between the total electronic energy and the free Gibbs energy in the gas phase estimated at the PBE0/6-31+G** level using PBE0/6-31+G** optimized geometry in the gas phase. Solution-phase optimizations were carried out with the Poisson−Boltzmann solver[15,16] implemented in the Jaguar v 6.5 suite of programs[17] using dielectric constant and the solvent probe radii for TFSA of 77.4 and 2.60 Å, respectively.

Since the PBE0 functional is not implemented directly in Jaguar 6.5, this functional was defined using the following keywords: idft = −1, xhf = 0.25, xexnl9 = 0.75, xcornl9 = 1.0, and xcorl4 = 1.0, which correspond to the definition of the PBE0 functional in the original paper[14] as 25% of the exact HF exchange, 75% of the PBE local and nonlocal exchange functional, the Perdew−Wang GGA-II 1991 local correlation functional, and the PBE local and nonlocal correlation functional. This model reproduces pK_a's of different acids with a maximum error of about 1 pK_a unit that corresponds to the error in the free Gibbs energy of 1.3 kcal/mol.[9]

Vertical ionization potentials (IP), electron affinities (EA), global electrophilicity indexes (ω^+), and local Fukui functions (f) of the reaction intermediates were calculated at the PBE0/6-31+G** level of theory. IP's and EA's were calculated as $E_{n-1} - E_n$ and $E_n - E_{n+1}$, respectively, where E_n is the total electronic energy of the n-electron system and E_{n-1} and E_{n+1} are the energies of the systems with $n - 1$ and $n + 1$ electrons, respectively. ω^+ was calculated according to ref 18 as $\mu^2/2\eta$, where μ is the chemical potential approximated as $-(IP + EA)/2$ and η is the chemical hardness approached as (IP − EA). The Fukui local functions at the sites for electrophilic and nucleophilic agents were approached by the gross natural charge (q) at site k (k = atom) for systems with $n - 1$ and $n + 1$ electrons, respectively, where n is the number of electrons in the studied species as $f_k^+ = q_k(n + 1) - q_k(n)$ and $f_k^- = q_k(n) - q_k(n - 1)$.[19] The global nucleophilicity was defined as $\omega^- = {}^1/_2(\mu^2\eta)$ and local electrophilicities and nucleophilicities indexes of the reactive sites were derived as $f_k^+\omega^+$ and $f^-\omega^-$, respectively. The definition of $\omega^- = -IP$ for global nucleophilicity suggested in ref 20 results in incorrect behavior for the local counterpart of global nucleophilicity; the quantity $f^-\omega^-$ drops with f^- due to the negative value of ω^-, which makes no sense. The definition of global nucleophilicity as ${}^1/_2(\mu^2\eta)$ corrects this deficiency, and it makes simple and intuitive chemical sense that nucleophilicity increases with a decrease of IP, EA, and η. This definition is easily derived from the well-proven expression for ω^+ and used in this paper for the analysis of the nucleophile properties.

SCHEME 3: Mono- and Diprotonated Forms of 4-Heterocyclohexanones and Cyclohexanone



Results and Discussion

Scheme 3 and Table 1 show the reactions of mono- and diprotonation as well as the corresponding free Gibbs energies in TFSA for different 4-heterocyclohexanones and cyclohexanone. It is seen that for all molecules except for **1b** the first protonation site is a carbonyl group. For **1b** the first protonation occurs at nitrogen with a very negative protonation energy of −31.15 kcal/mol. In all cases the energies of the first protonation are quite negative, implying that monocations are the dominant species in TFSA solution. The second protonation occurs at carbonyl oxygen in the case of **1b** and at heteroatoms for **1c**,**d**. In the case of **1a** the second protonation occurs at an already-protonated carbonyl and this intermediate will not be considered further due to the very positive ΔG = 39.06 kcal/mol. Unlike the first protonation the free Gibbs energies of the second protonation are positive. Since these values are only moderately positive, there must be a reasonable concentration of diprotonated molecules in the TSFA solution to have a noticeable effect on the reactivity of 4-heterocyclohexanones. Thus, the calculated protonation free Gibbs energy of 2,2,2-trifluormethylacetophenone in TSFA is of 7.8 kcal/mol, [9] and this molecule readily

TABLE 1: Calculated Protonation (ΔG_p) of the Free Gibbs Energies of Different Molecules in TFSA (kcal/mol)

reaction	ΔG_p
1a + CF_3SO_3H → **4a** + $CF_3SO_3^-$	−5.97
1b + CF_3SO_3H → **4b** + $CF_3SO_3^-$	−5.70
1c + CF_3SO_3H → **4c** + $CF_3SO_3^-$	−3.97
1d + CF_3SO_3H → **4d** + $CF_3SO_3^-$	−3.59
1b + CF_3SO_3H → **2b** + $CF_3SO_3^-$	−31.15
1c + CF_3SO_3H → **2c** + $CF_3SO_3^-$	−0.88
1d + CF_3SO_3H → **2d** + $CF_3SO_3^-$	−2.83
2b + CF_3SO_3H → **3b** + $CF_3SO_3^-$	0.18
4c + CF_3SO_3H → **3c** + $CF_3SO_3^-$	6.76
4d + CF_3SO_3H → **3d** + $CF_3SO_3^-$	2.60
9a + CF_3SO_3H → **12a** + $CF_3SO_3^-$	3.85
9b + CF_3SO_3H → **12b** + $CF_3SO_3^-$	4.56
9b + CF_3SO_3H → **10b** + $CF_3SO_3^-$	−32.90
12b + CF_3SO_3H → **11b** + $CF_3SO_3^-$	9.34
9c + CF_3SO_3H → **12c** + $CF_3SO_3^-$	6.24
9c + CF_3SO_3H → **10c** + $CF_3SO_3^-$	−1.75
10c + CF_3SO_3H → **11c** + $CF_3SO_3^-$	10.66
9d + CF_3SO_3H → **12d** + $CF_3SO_3^-$	6.49
9d + CF_3SO_3H → **10d** + $CF_3SO_3^-$	−6.96
10d + CF_3SO_3H → **11d** + $CF_3SO_3^-$	10.53

TABLE 2: Free Gibbs Activation (ΔG_a) and Formation Energies of (ΔG) of Studied Reactions (kcal/mol)

run	reaction	ΔG_a	ΔG
1	**4a** + 2biphenyl (benzene) = **5a** + $H3O^+$		−4.81 (8.18)
2	**3b** + 2biphenyl (benzene) = **6b** + $H3O^+$		−1.94 (−1.56)
3	**4c** + 2biphenyl = **5c** + $H3O^+$		3.84
4	**4d** + 2biphenyl = **5d** + $H3O^+$		3.02
5	**3c** + 2biphenyl = **6c** + $H3O^+$		−4.21
6	**3d** + 2biphenyl = **6d** + $H3O^+$		−2.92
7	**4a** + biphenyl (benzene) = **7a**	33.2	32.3 (36.2)
8	**3b** + biphenyl (benzene) = **8b**	27.4	24.1 (30.3)
9	**4c** + biphenyl = **7c**	31.8	30.4
10	**4d** + biphenyl = **7d**	32.0	31.9
11	**3c** + biphenyl = **8c**	26.0	21.7
12	**3d** + biphenyl = **8d**	26.6	22.9

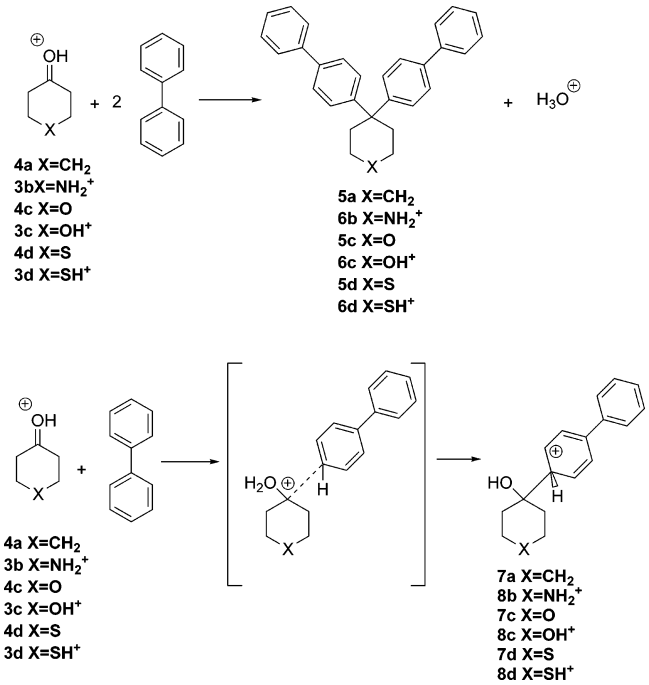
participates in TFSA mediated polycondensation with aromatic hydrocarbons showing that the concentration of protonated species is high enough for the polyhydroxyalkylation reaction to occur.

Since the protonation of a carbonyl group is a necessary condition for aldehydes and ketones to be active in electrophilic substitution reactions, ketones **1a**,**c**,**d** meet this requirement after the first protonation, while in the case of **1b** the protonation of a carbonyl is a second protonation reaction. Therefore, in the case of ketones **1a**,**b**, there is only one intermediate for each molecule (**4a** and **3b**, respectively), potentially active in the electrophilic substitution reactions, while for 4-heterocyclohexanones **1c**,**d** both mono- and diprotonated molecules **4c**,**d** and **3c**,**d** are potentially active species.

The enhanced reactivity of diprotonated species can be related to the thermodynamic factor, kinetic factors, or both. It is accepted that the formation of an σ-complex is the rate-determining step in the reactions of aromatic electrophilic substitution.[21] Therefore, we use the free Gibbs activation energy of σ-complex formation between the corresponding electrophile and biphenyl, a common monomer in the reaction of TFSA mediated polycondensation, as a measure of the effect of the electrophilic nature on the kinetics of polyhydroxyalkylation, and the free Gibbs reaction energies shown in Scheme 4 as a measure of the electrophilic nature effect on thermodynamics.

As seen from Table 2 (runs 1−6) reactions involving monoprotonated species (**4a**−**d**) are endergonic for all ketones except for **1a**. On the other hand, for all reactions involving diprotonated species ΔG are negative. This favorable effect of

SCHEME 4: Reactions of Biphenyl with 4-Heterocyclohexanones and Cyclohexanone



diprotonation on the reaction thermodynamics is due to the difference in protonation energies of heteroatom in dications **3c**,**d** and products **6c**,**d**. The protonation energies of heteroatoms in products **6c**,**d** are more negative than these in **3c**,**d** due to nonexistent electrostatic repulsion between protons in the former. This effect can be estimated directly from the free Gibbs reaction energies (runs 3−6): 8.11 and 5.94 kcal/mol for oxygen and sulfur atoms, respectively. In the case of piperidone the **1b** monoprotonated intermediate is not active in the hydroxyalkylation reaction.

According to calculations, both reactions 1 and 2 are exergonic while experiment shows that cyclohexanone (**1a**) does not participate in the reaction of hydroxyalkylation with benzene while **1b** gives the reaction product in a high yield.[12] We estimated ΔG of reactions 1 and 2 with benzene as nucleophile (Table 2). As seen the result show that in case of benzene, reaction 1 is endergonic while the reaction 2 is exergonic in accordance with experimental data. Since the gas phase ΔG calculated at PBE0/6-31+G** level give 44.1 and 43.2 kcal/mol for the reactions **4a** + 2biphenyl and **4a** + 2benzene, respectively, the conclusion is that solvation is the primary factor influencing the reaction thermodynamics in these cases.

It has been recently shown that the free Gibbs reaction and activation energies of hydroxyalkylation reactions are in good correlation with the EA of the electrophile and in the case of different electrophiles and nucleophiles with the difference of EA of electrophile and IP of nucleophile.[22]

Table 2 (runs 7−12) shows the free Gibbs activation and reaction energies of the σ-complexes formation. It is clearly seen that there is a correlation between the electronegativity of the atom in position 4 and the free Gibbs activation and reaction energies of σ-complexes formation in the case of monoprotonated species. The energies dropped with an increase of their electronegativity from carbon to sulfur and oxygen. However, this effect is rather small, and all monoprotonated electrophiles have their activation and reaction energies of σ-complex formation within 2 kcal/mol. The protonation of heteroatoms result in a substantial decrease of both the free Gibbs activation

TABLE 3: Vertical Ionization Potentials (IP), Electron Affinities (EA, eV), Electrophilic (f^+) and Nucleophilic (f^-) Fukui Functions of Carbonyl Carbon and β sp^2 Enol Carbon, Respectively, Local Nucleophilicity ($f^-\omega^-$) and Electrophilicity ($f^+\omega^+$) of the Reactive Sites in Nucleophiles and Electrophiles, Natural Charges at Carbonyl Carbon (q), and LUMO Energies of Studied Electrophiles at the PBE0/6-31+G Level**

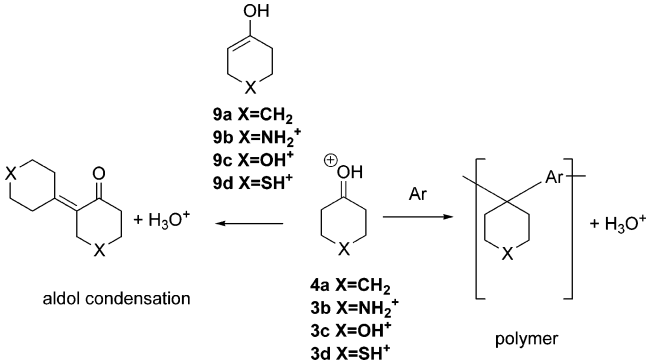
molecule	IP	EA	f^+	f^-	$f^-\omega^- \times 10^4$	$f^+\omega^+$	q	LUMO
3b	21.83	9.99	0.426	–	–	4.55	0.722	−12.14
4a	15.96	5.38	0.436	–	–	2.35	0.714	−7.42
4c	14.92	5.55	0.405	–	–	2.26	0.674	−7.57
3c	22.18	10.18	0.423	–	–	4.79	0.723	−12.34
4d	13.16	5.70	0.429	–	–	2.56	0.706	−7.69
3d	21.17	10.04	0.431	–	–	4.71	0.724	−12.15
benzene	9.32	−1.60		0.120	3.68	–	–	–
biphenyl	8.15	−0.53	–	0.148	5.88		–	–
9a	8.04	−1.23	–	0.347	16.14	–	–	–
9b	12.88	3.41	–	0.376	2.99	–	–	–
9c	13.38	3.61	0.391	2.77	–	–		
9d	13.10	3.45	0.388	2.93	–	–		

and formation energies for σ-complexes as seen from Table 2, reflecting higher reactivity of diprotonated species. Thus, according to calculations, dications **3c**,**d** are even more active than **3b** derived from 4-piperidone, and, therefore, 4-heterocyclohexanones **1c**,**d** can be considered promising monomers for superacid mediated polymer synthesis.

Table 3 shows calculated reactivity indexes of electrophiles and nucleophiles involved in this study. There is a very good correlation (correlation coefficient of 0.986) between EA's and the local electrophilicity of the carbonyl carbon atom and the free Gibbs activation and reaction energies of the σ-complex formation for the electrophiles listed in Table 3. The second protonation increases significantly both the electrophilicity of the carbonyl atom and the EA of the electrophile, which is reflected in the reduction of both the free Gibbs activation and the reaction energies of σ-complexes formation for diprotonated intermediates. Higher free Gibbs activation and reaction energies of σ-complexes formation in the case benzene compared to biphenyl (Table 2) can be rationalized in terms of a lower local nucleophilicity or a higher IP of benzene compared to biphenyl (Table 3). It is interesting to note that calculated natural charges of carbonyl carbons are very similar for mono- and dicationic electrophiles, implying that the nature of the carbonyl activation in dications has little to do with the electrostatic through-space effect. On the other hand, the second protonation markedly lowers LUMO energies similar to the effect of electron-withdrawing substituents.[8] This finding favors the suggestion that inductive and not through-space effect is the most important factor enhancing the carbonyl activity of diprotonated species.

Authors demonstrated[12] that in the case of reaction of **1a** with benzene a small amount of aldol condensation product was formed while for **1b** the only isolated product was diphenylpiperidine.

SCHEME 5: Competition between Polycondensation and Aldol Condensation

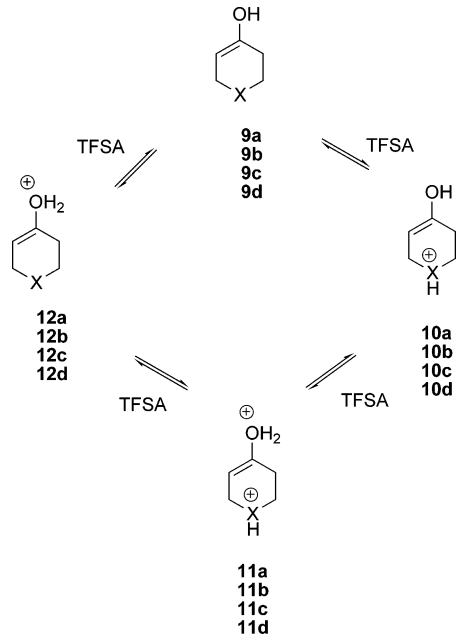


In fact, the aldol condensation is an undesirable side reaction interfering with polycondensation since strong acidic conditions favor the enol formation and enol competes with the aromatic hydrocarbon for the electrophile (Scheme 5)

Scheme 6 and Table 1 show the protonation reactions of enols in TFSA and their free Gibbs energies, respectively. As seen, in all cases the first protonation occurs at the ring heteroatom and these reactions are exergonic. The second proton goes to the hydroxyl oxygen, and this reaction is endergonic for all enols. Even in the case of enol **9a**, where the protonation of the hydroxyl oxygen is the first protonation, the reaction is endergonic. Therefore, most of the enol molecules exist in the form of **9a**−**d** in TFSA solution.

Data listed in Table 3 allow us to explain these experimental data in terms of electronic properties of involved electrophiles and nucleophiles as well as predict the reactivity of other 4-heterocyclohexanones. Since the hydrohyalkylation and aldol condensation involve the same electrophile, the rate of these reactions is determined by the nucleophilic nature. As seen from Table 3, enol **9a** is a much stronger nucleophile compared to benzene, as follows from its lower IP and higher nucleophilicity of the reactive β carbon. Therefore, in the case of **1a** the aldol condensation prevails in accordance with experimental data. On the other hand, enol **9b** is far less nucleophilic than benzene

SCHEME 6: Mono- and Diprotonated Forms of Enols of 4-Heterocyclohexanones and Cyclohexanone



due to the protonated nitrogen atom (higher IP and lower local nucleophilicity) and cannot compete with benzene for the electrophile.

As seen from Table 3 a similar situation holds for enols **9c**,**d**. They are much weaker nucleophiles compared with benzene and biphenyl; therefore they would not interfere with polyhydroxyalkylation.

Conclusions

Calculations validate the hypothesis of the existence of diprotonated reactive intermediates in TFSA solutions of 4-heterocyclohexanones, where both carbonyl oxygen and heteroatom are protonated. Diprotonated and not monoprotonated 4-heterocyclohexanones are the reactive species in hydroxyalkylation reaction. Second protonation affects both the thermodynamics and kinetics of hydroxyalkylation, reducing the free activation and reaction energies of the reaction. Increased reactivity of diprotonated molecules is related to the lowering of LUMO energy similar to the effect of electron-withdrawing substituents supporting the hypothesis that carbonyl group activation is due to the inductive effect of a protonated heteroatom and not through-space electrostatic effect. In addition the protonation of a heteroatom reduces the possibility of aldol condensation byproduct formation due to a decline of enol electrophilicity involved in the aldol condensation.

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