Conformational Investigations of HMPAO Isomers and Their Zinc(II) Complexes

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Isomers based on the RS and EZ geometrical isomerism of the neutral, deprotonated species of HMPAO and their complexes with zinc(II) ion have been investigated by semiempirical AM1 optimization method. The Hartree-Fock energies on AM1 geometries of HMPAO species were calculated with HF/6-31G* methods. Twenty-two isomers of the neutral and twenty isomers of the deprotonated species of HMPAO have been found. The presence of four EE-series isomers of both zinc(II) complexes with the neutral and deprotonated HMPAO have been expected and the SREE typical isomer of both types of complexes is the most stable isomer. Energies of complexation of zinc(II)/HMPAO isomers with AM1 geometries were calculated by HF/6-31G* method. Due to the complexations with zinc(II), the structural reorganizations of some isomers of the neutral HMPAO have been occurred. The optimized geometrical parameters of the related conformations have been discussed in terms of their stabilities and existences.

Keywords : HMPAO, Isomers, Zinc complex, AM1, Conformations.

Introduction

HMPAO (hexamethylpropylene amine oxime) has been known as a ligand forming complex with technetium-99m as radiomedical reagent for the medical use.[1] Technetium-99m/HMPAO complex was used in SPECT, SPET and MRI applications for brain treatments.[1,2] According to the geometries of HMPAO isomers, their complexes with transition metals particularly with technetium-99m can be formed as Tc-D,D- and Tc-L,L-HMPAO isomers.[3] In order to obtain the useful and specific isomer for medical examination, the stereoselective isomer of HMPAO such a d,l-HMPAO was synthesized and researched.[4,5]

To get more understanding on HMPAO isomers and their complexation with transition metals, the structural information of HMPAO and their related species could be investigated. In the present work, the geometrical investigation of HMPAO isomers and their zinc(II) complexes has been, theoretically attempted using quantum mechanical calculations. Zinc(II) ion has been selected as an appropriate divalent transition metal to form complexes with different geometries of HMPAO in order to obtain preliminary information for further study of their stereoselective synthesis and complexes with radiochemical cations.

Methods

Most stable conformations of neutral and deprotonated forms of HMPAO for each possible types of isomers which defined by the RS/EZ geometrical isomerism were carried out by geometry optimization using semiempirical AM1 method.[7] The single-point energies of the optimized geometries of HMPAO computed by *ab initio* calculations with HF/3-21G[8,9] and HF/6-31G*[8] methods were obtained. The energies of zinc(II) complexes with neutral and deprotonated HMPAO were computed by Hartree-Fock method using 6-31G* basis set and derived from the Hartree-Fock energies at 3-21G theoretical level including counterpoise corrections. All calculations were performed with Gaussian 94 program.[10]

Neutral, deprotonated forms of HMPAO and hydroxyl proton, are denoted by LH_2, LH^- and H^+, respectively. Therefore, the process of deprotonation, complexation for divalent transition metal such a Zn^{2+} with neutral and deprotonated species of HMPAO can be written as eqs. (1), (2) and (3), respectively.

$$LH_2 \rightleftarrows LH^- + H^+ \tag{1}$$

$$LH^- + Zn^{2+} \rightleftarrows ZnLH^+ \tag{2}$$

$$LH_2 + Zn^{2+} \rightleftarrows ZnLH_2^{2+} \tag{3}$$

Energies of complexation for zinc(II) complexes with neutral ($\Delta E^0_{complex}$) and deprotonated ($\Delta E^1_{complex}$) HMPAO can be calculated according eqs. (4) and (5), respectively.

$$\Delta E^0_{complex} = E_{ZnLH_2^{2+}} - E_{LH_2} - E_{Zn^{2+}} \tag{4}$$

$$\Delta E^1_{complex} = E_{ZnLH^+} - E_{LH^-} - E_{Zn^{2+}} \tag{5}$$

Counterpoise corrections of Boys and Bernardi[11] were applied for energy improvement by eliminating the basis set superposition error (BSSE). The BSSE energies of complexation ($\Delta E_{complex,BSSE}$)[12] based on the neutral and deprotonated HMPAO were evaluated by eqs. (6) and (7), respectively.

$$\Delta E^0_{complex,BSSE} = E_{ZnLH_2^{2+}} - E_{LH_2,BSSE} - E^0_{Zn^{2+},BSSE} \tag{6}$$

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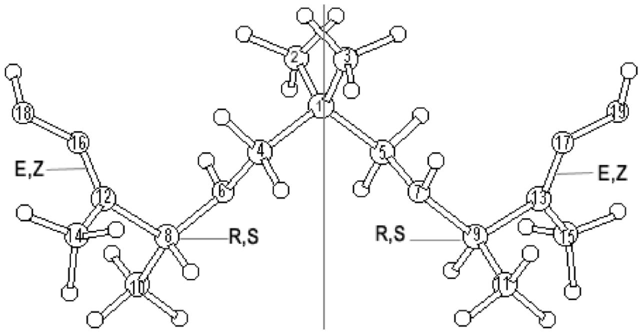


Figure 1. Definition of typical isomers of HMPAO according to the RS/EZ geometrical isomerism, specified by the XYAB isomeric formula, where X (R or S), A (E or Z) and Y (R or S), B (E or Z) represent the left and right parts of HMPAO molecule, respectively. (R, S defined at the left and right parts of HMPAO molecule according to the tetrahedral C8 and C9 centers, respectively. E, Z defined at the left and right parts of HMPAO molecule according to the C12=N16 and C13=N17 bonds, respectively.)

$$\Delta E^{1}_{complex,BSSE} = E_{ZnLH^{+}} - E_{LH^{-},BSSE} - E^{1}_{Zn^{2+},BSSE} \qquad (7)$$

where $E_{LH^2,BSSE}$ and $E^{0}_{Zn^{2+},BSSE}$ are the energies for LH_2 with a set of ghost orbital on Zn^{2+} position of the $ZnLH_2^{2+}$ geometry and Zn^{2+} with a set of ghost orbital on LH_2 position of the $ZnLH_2^{2+}$ geometry, respectively. and are the energies for LH^- with a set of ghost orbital on Zn^{2+} position of the $ZnLH^+$ geometry and Zn^{2+} with a set of ghost orbital on LH^- position of the $ZnLH^+$ geometry , respectively.

Method of search for stereoisomeric conformations of neutral and deprotonated forms of HMPAO is by scanning for the lowest energy conformations using the AM1-geometry optimization. All possible isomers have been considered and defined by a symbolic formula of XYAB based on the RS/EZ geometrical isomerism as described in Figure 1. According to the fixed positions of four variables X, Y, A and B in the XYAB isomeric formula at two possibilities for each variables (X=R or S, Y=R or S, A=E or Z and B=E or Z), then the combination number which is the number of basic conformations, is equal to sixteen. Because of this basis, geometries and number of their isomers have to be investigated under consideration of these sixteen conformational types. The sixteen basic conformations of typical isomers are RREE, RREZ, RRZE, RRZZ, RSEE, RSEZ, RSZE, RSZZ, SREE, SREZ, SRZE, SRZZ, SSEE, SSEZ, SSZE and SSZZ. The isomers of zinc(II) complexes with different conformations of HMPAO were obtained by consideration of the lowest energy conformation for each typical isomers by comparing their optimized geometrical parameters with x-ray crystal data.[13]

Results and Discussion

According to the AM1-optimizations on the neutral

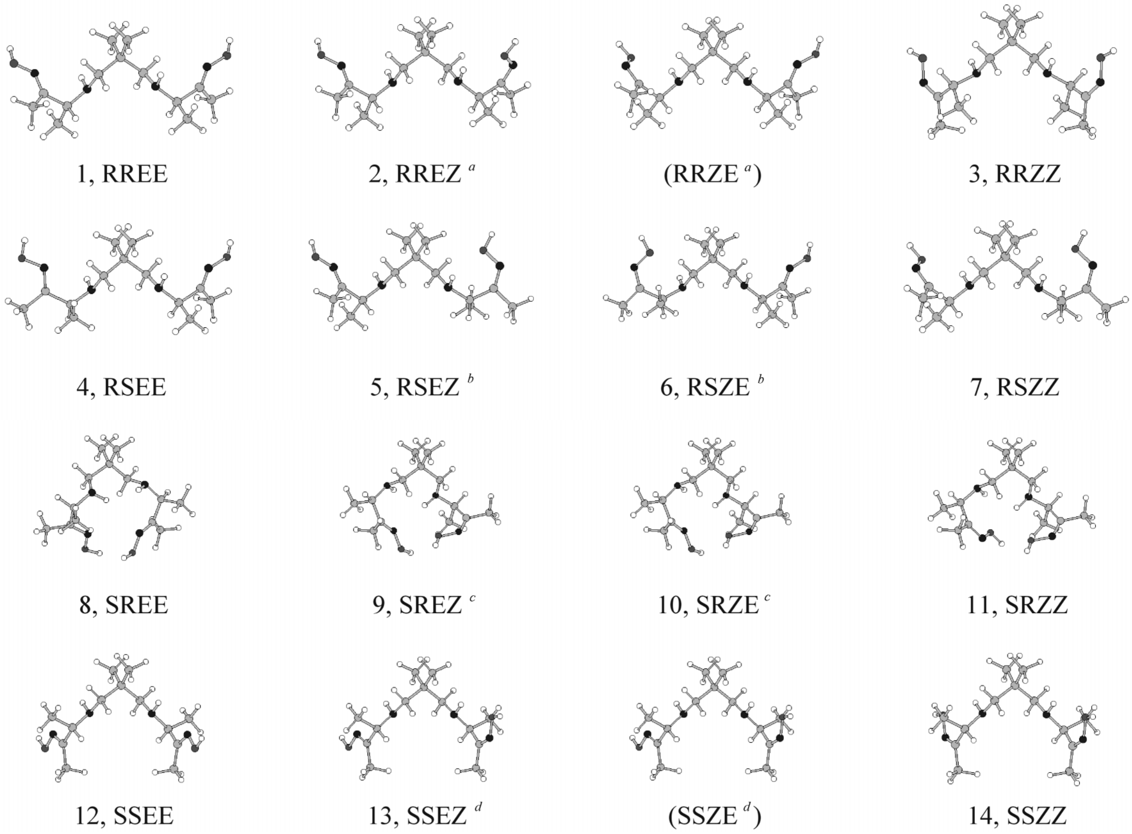

1, RREE
2, RREZ [a]
(RRZE [a])
3, RRZZ
4, RSEE
5, RSEZ [b]
6, RSZE [b]
7, RSZZ
8, SREE
9, SREZ [c]
10, SRZE [c]
11, SRZZ
12, SSEE
13, SSEZ [d]
(SSZE [d])
14, SSZZ

Figure 2. Fourteen isomers of neutral HMPAO, obtained from AM1 geometry optimization. ([a]RREZ and RRZE are identical, [b]RSEZ and RSZE are enantiomers, [c]SREZ and SRZE are enantiomers, [d]SSEZ and SSZE are identical)

Table 1. The Hartree-Fock energies of neutral and deprotonated HMPAO with HF/6-31G* methods and relative energies of their isomers

Isomers	E(HF/6-31G*)[a]	Rel. energies[b,c] of HF/6-31G*
	neutral form, LH$_2$	
RREE	-875.916760553	0.0
RREZ (RRZE)	-875.916287807	0.3
RRZZ	-875.906513573	6.4
RSEE	-875.909636452	4.5
RSEZ[d]	-875.900244513	10.4
RSZE[d]	-875.900244513	10.4
RSZZ	-875.899714346	10.7
SREE	-875.913592773	2.0
SREZ[e]	-875.912608646	2.6
SRZE[e]	-875.912608646	2.6
SRZZ	-875.913907973	1.8
SSEE	-875.911144034	3.5
SSEZ (SSZE)	-875.911333939	3.4
SSZZ	-875.911323375	3.4
	deprotonated form, LH$^-$	
RREE[f]	-875.309789774	9.4
RREZ[g]	-875.304125258	12.9
RRZE[h]	-875.307588399	10.8
RRZZ[i]	-875.312340760	7.8
RSEE	-875.299139717	16.1
RSEZ[j]	-875.303844984	13.1
RSZE[j]	-875.303844984	13.1
RSZZ	-875.308951359	9.9
SREE	-875.318047663	4.2
SREZ[k]	-875.324756825	0.0
SRZE[k]	-875.324756825	0.0
SRZZ	-875.319017152	3.6
SSEE[f]	-875.309789774	9.4
SSEZ[h]	-875.307588399	10.8
SSZE[g]	-875.304125258	12.9
SSZZ[i]	-875.312340760	7.8

[a]energies in hartree, [b]ΔE in kcal/mol relative to most stable isomer of neutral species, [c]ΔE in kcal/mol relative to most stable isomers of deprotonated species, [d,e,f,g,h,i,j,k]to be enantiomers

species of HMPAO and the isomer identification, fourteen isomers of the neutral species have been obviously found as shown in Figure 2. Their geometries of the RREZ and SSEZ isomers are identical to the RRZE and SSZE isomers,

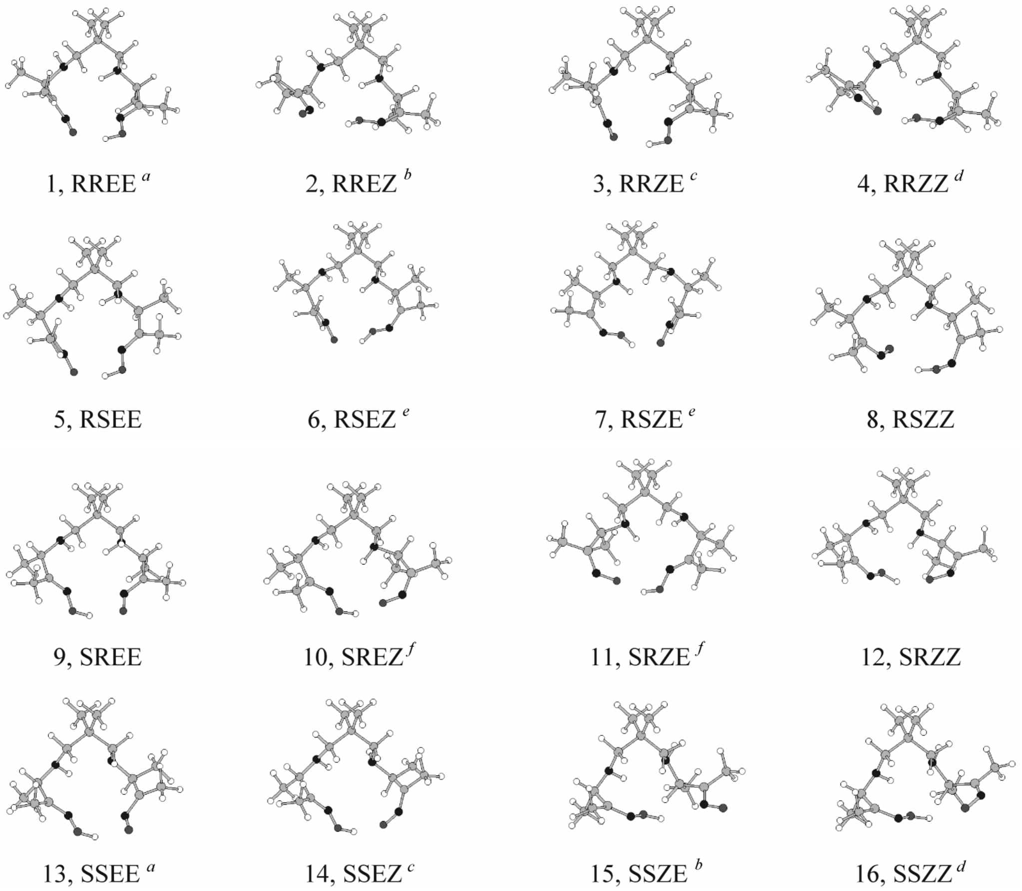

1, RREE [a] 2, RREZ [b] 3, RRZE [c] 4, RRZZ [d]
5, RSEE 6, RSEZ [e] 7, RSZE [e] 8, RSZZ
9, SREE 10, SREZ [f] 11, SRZE [f] 12, SRZZ
13, SSEE [a] 14, SSEZ [c] 15, SSZE [b] 16, SSZZ [d]

Figure 3. Sixteen isomers of deprotonated HMPAO, obtained from AM1 geometry optimization. ([a]RREE and SSEE, [b]RREZ and SSZE , [c]RRZE and SSEZ, [d]RRZZ and SSZZ, [e]RSEZ and RSZE, [f]SREZ and SRZE are enantiomers.)

Table 2. Geometry-optimized structures of fourteen and sixteen typical isomers for neutral and deprotonated HMPAO respectively, specified by dihedral angles of ϕ (C1-C4-N6-C8), χ (C4-N6-C8-C12), θ (N6-C8-C12-N16), ω (C8-C12-N16-O18), ψ (C10-C8-C12-C14), ϕ' (C1-C5-N7-C9), χ' (C5-N7-C9-C13), θ' (N7-C9-C13-N17), ω' (C9-C13-N17-O19) and ψ' (C11-C9-C13-C15)

Isomers	ϕ	χ	θ	ω	ψ	ϕ'	χ'	θ'	ω'	ψ'	group
neutral form, LH_2											
RREE	178.6	62.9	41.8	179.0	94.8	178.6	62.9	41.8	179.0	94.8	C_2
RREZ [a]	-172.1	62.8	41.8	179.0	94.8	178.6	61.4	51.7	-0.7	105.3	C_1
RRZE [a]											
RRZZ	-175.0	171.9	58.5	-0.5	110.2	-175.0	171.9	58.5	-0.5	110.2	C_2
RSEE	179.0	62.9	41.8	179.0	94.8	-174.4	85.0	-20.4	-179.9	-69.5	C_1
RSEZ [b]	-170.8	101.1	-41.4	0.7	-90.4	178.6	62.9	41.8	179.0	94.8	C_1
RSZE [b]	178.6	62.9	41.8	179.0	94.8	-170.8	101.1	-41.4	0.7	-90.4	C_1
RSZZ	178.8	61.3	51.6	-0.7	105.2	-170.9	101.1	-41.3	0.7	-90.3	C_1
SREE	175.2	-62.8	-47.8	-179.0	-100.5	-170.3	66.5	41.5	178.8	94.9	C_1
SREZ [c]	170.2	-63.8	-47.8	179.0	-101.2	172.5	59.2	53.0	0.4	106.6	C_1
SRZE [c]	-172.5	-59.2	-53.0	-0.4	-106.6	-170.2	63.8	47.8	-179.0	101.2	C_1
SRZZ	175.2	-59.9	-50.2	0.3	-103.2	171.5	61.4	52.9	0.3	106.7	C_1
SSEE	174.3	-172.4	-59.2	-179.2	-110.2	174.3	-172.4	-59.2	-179.2	-110.2	C_2
SSEZ [d]	174.3	-172.4	-59.2	-179.2	-110.2	174.3	-172.4	-59.2	0.6	-110.2	C_1
SSZE [d]											
SSZZ	175.0	-171.9	-58.5	0.5	-110.2	175.0	-171.9	-58.5	0.5	-110.2	C_2
deprotonated form, LH^-											
RREE [e]	172.7	-40.3	-82.3	177.8	-32.6	170.2	62.0	52.5	179.4	106.4	C_1
RREZ [f]	154.9	44.2	-104.1	179.3	-52.5	-159.8	56.8	50.0	1.3	103.5	C_1
RRZE [g]	175.9	-38.8	-95.2	-0.6	-40.8	-170.1	62.9	52.6	-179.5	107.3	C_1
RRZZ [h]	-167.1	-59.8	-52.3	1.3	-107.0	-178.2	56.7	47.4	1.4	100.5	C_1
RSEE	171.9	-69.0	-69.1	179.0	-19.2	-175.1	56.7	69.5	178.7	19.5	C_1
RSEZ [i]	173.2	-56.7	-68.0	178.6	-17.6	178.8	68.4	71.3	3.7	22.8	C_1
RSZE [i]	-178.8	-68.4	-71.3	-3.7	-22.8	-173.2	56.7	68.0	-178.6	17.6	C_1
RSZZ	167.3	-58.6	-50.2	2.4	3.2	172.0	67.8	84.2	5.9	35.5	C_1
SREE	176.4	-60.7	-44.5	-178.7	-97.8	-176.0	62.0	52.0	-179.8	106.0	C_1
SREZ [j]	166.9	-59.5	-41.6	-180.0	-95.2	162.0	64.5	61.8	1.3	117.8	C_1
SRZE [j]	-162.0	-64.5	-61.8	-1.3	-117.8	-166.9	59.5	41.6	180.0	95.2	C_1
SRZZ	178.1	-56.8	-47.4	-1.4	-100.5	167.1	59.8	52.6	-1.3	133.0	C_1
SSEE [e]	-170.2	-62.0	-52.5	-179.4	-106.4	-172.7	40.3	82.3	-177.8	32.6	C_1
SSEZ [g]	170.1	-62.9	-52.6	179.5	-107.3	-175.9	38.8	95.2	0.6	40.8	C_1
SSZE [f]	159.8	-56.8	-50.0	-1.3	-103.5	-154.9	-44.2	104.1	-179.3	52.5	C_1
SSZZ [h]	178.2	-56.7	-47.4	-1.4	-100.5	167.1	59.8	52.3	-1.3	107.0	C_1

[a,d] to be identical, [b,c,e,f,g,h,i,j] to be enantiomers

respectively. Their total energies of two pairs of neutral species isomers are equivalent (Table 1). Sixteen geometrical isomers of the deprotonated species of HMPAO and their total energies of six pairs of enantiomers are shown in Figure 3 and Table 1, respectively. The optimized geometries of possible isomers of the neutral and deprotonated species of HMPAO, specified by dihedral angles of ϕ (C1-C4-N6-C8), χ (C4-N6-C8-C12), θ (N6-C8-C12-N16), ω (C8-C12-N16-O18), ψ (C10-C8-C12-C14), ϕ' (C1-C5-N7-C9), χ' (C5-N7-C9-C13), θ' (N7-C9-C13-N17), ω' (C9-C13-N17-O19) and ψ' (C11-C9-C13-C15) are listed in Table 2. Due to the consideration of the optical isomerism on the basic conformations of HMPAO, all stereoisomers of the neutral species are actually the RREE, RRZZ, RSEE, RSZZ, SREE, SRZZ, SSEE, SSZZ and their enantiomers, RREZ (or RRZE), SSEZ (or SSZE), RSEZ, RSZE (enantiomer of RSEZ), SREZ and SRZE (enantiomer of SREZ); there are totally twenty-two isomers. The stereoisomers of deprotonated HMPAO are totally twenty isomers namely the RSEE, RSZZ, SREE, SRZZ and their enantiomers, RREE, SSEE (enantiomer of RREE), RREZ, SSZE (enantiomer of RREZ), RRZE, SSEZ (enantiomer of RRZE), RRZZ, SSZZ (enantiomer of RRZZ), RSEZ, RSZE (enantiomer of RSEZ), SREZ, SRZE (enantiomer of SREZ).

The ω (C8-C12-N16-O18) and ω' (C9-C13-N17-O19) dihedral angles (Table 2) approach 180 and 0 degrees that correspond to the E and Z typical isomers, respectively. The RREE, RRZZ, SSEE and SSZZ isomers of the neutral HMPAO are in C2 symmetry, otherwise C1, that correspond to the identical set of dihedral angles at the left and right of molecular parts (Figure 1). Absolute values of the ϕ (C1-C4-N6-C8) and ϕ' (C1-C5-N7-C9) of either the ligand or the

Table 3. Optimized geometrical parameters of the lowest energies structures of Zn(II) complexes with the neutral ($ZnLH_2^{2+}$), deprotonated ($ZnLH^+$) species of HMPAO and Zn-N bond length, obtained by AM1 method

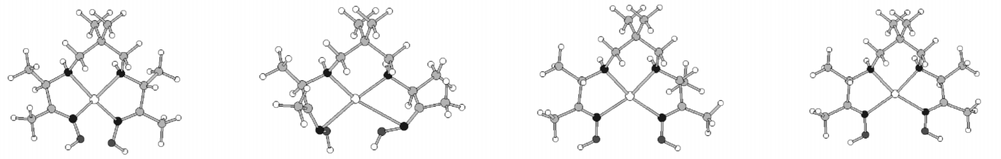
Isomers	ϕ	χ	θ	ω	ψ	ϕ'	χ'	θ'	ω'	ψ'	Zn-N[a]
					$ZnLH_2^{2+}$						
RREE [b]	174.8	-86.5	-19.0	180.0	34.1	172.5	146.9	-9.3	179.0	45.8	2.146
RREZ [c]	-170.3	-59.9	-66.1	-0.6	-13.2	176.7	115.7	7.2	-178.8	61.1	3.117
RRZE [d]	-164.6	-47.1	-65.5	-0.4	-13.5	177.7	134.7	2.3	176.1	55.0	3.249
RRZZ [e]	-169.9	-62.3	-66.1	-1.7	-13.8	-174.8	44.5	59.9	-0.2	115.1	3.293
RSEE	-174.7	-86.8	-19.3	-179.9	33.8	173.4	158.2	-22.1	179.9	-74.4	2.155
RSEZ [f]	-172.6	-59.5	-65.5	-0.7	-12.4	173.6	99.3	9.3	179.8	-43.0	3.123
RSZE [f]	-173.6	-99.3	-9.3	-179.8	43.0	172.6	59.5	65.5	0.7	12.4	3.123
RSZZ	-173.3	-72.6	-66.1	-0.5	-13.7	178.5	55.2	62.5	0.9	8.7	3.172
SREE	-171.2	-147.6	9.0	178.8	-46.0	174.3	98.1	15.6	-171.4	69.5	2.148
SREZ [g]	-171.1	-134.6	4.1	179.5	-50.5	177.4	42.9	54.2	-5.5	108.8	3.365
SRZE [g]	-177.4	-42.9	-54.2	5.5	-108.8	171.1	134.6	-4.1	-179.5	50.5	3.365
SRZZ	-168.7	-71.9	-58.7	-2.3	-111.6	-174.9	44.7	60.2	-0.1	115.5	3.293
SSEE [b]	-172.5	-146.9	9.3	-179.0	-45.8	-174.8	86.5	19.0	-180.0	-34.1	2.146
SSEZ [d]	-177.7	-134.7	-2.3	-176.1	-55.0	164.6	47.1	65.5	0.4	13.5	3.249
SSZE [c]	-176.7	-115.7	-7.2	178.8	-61.1	170.3	59.9	66.1	0.6	13.2	3.117
SSZZ [e]	174.8	-44.5	-59.9	0.2	-115.1	169.9	62.3	66.1	1.7	13.8	3.293
$ZnLH^+$											
RREE [h]	171.8	105.0	12.9	178.7	66.2	179.5	-84.1	-33.3	-175.8	24.2	2.196
RREZ [i]	-177.7	-54.7	-61.8	1.4	-8.7	167.6	146.5	-11.5	178.8	43.5	2.874
RRZE [j]	-174.7	-57.5	-61.5	1.5	-8.5	168.4	130.8	1.8	178.5	95.5	2.867
RRZZ [k]	178.8	-56.6	-62.8	0.6	-9.9	174.3	42.3	67.5	0.9	122.7	3.470
RSEE	177.6	-82.8	-33.5	-176.8	23.9	169.6	86.1	20.3	177.5	-32.9	2.216
RSEZ [l]	177.9	-54.5	-62.1	1.2	-9.1	170.1	162.9	-28.8	179.7	-82.3	2.871
RSZE [l]	-170.1	-162.9	28.8	-179.7	82.3	-177.9	54.5	62.1	-1.2	9.1	2.871
RSZZ	176.5	-59.0	-62.9	0.8	-9.7	168.5	50.5	68.8	0.8	15.8	3.317
SREE	179.8	98.2	24.9	177.4	76.0	-171.4	-107.4	-12.8	-178.6	-66.0	2.193
SREZ [m]	-165.6	146.4	13.3	-178.3	-41.7	-178.2	53.6	55.7	-1.9	110.3	2.897
SRZE [m]	178.2	-53.6	-55.7	1.9	-110.3	165.6	-146.4	-13.3	178.3	41.7	2.897
SRZZ	177.6	28.0	-86.8	2.8	-139.1	-178.6	53.0	55.7	-2.3	110.4	4.748
SSEE [h]	-179.5	84.1	33.3	175.8	-24.2	-171.8	-105.0	-12.9	-178.7	-66.2	2.196
SSEZ [j]	-168.4	-130.8	-1.8	-178.5	-95.5	174.7	57.5	61.5	-1.5	8.5	2.867
SSZE [i]	-167.6	-146.5	11.5	-178.8	-43.5	177.7	54.7	61.8	-1.4	8.7	2.874
SSZZ [k]	-174.3	-42.3	-67.5	-0.9	-122.7	-178.8	56.6	62.8	-0.6	9.9	3.470

[a] distance in Å, [b,c,d,e,f,g,h,i,j,k,l,m] to be enantiomers

complex isomers approach 180 degree which indicate the stabilities of their geometries as shown in Table 2 and 3. The total energies of the neutral and deprotonated species of HMPAO with HF/6-31G* methods and their relative energies derived from HF/6-31G* energies listed in Table 1 show that the most stable isomers for the neutral and deprotonated HMPAO are the RREE and SREZ (or SRZE), respectively. Deprotonations of the neutral RREE, RREZ, RRZE, RRZZ, RSEE, RSEZ, RSZE, RSZZ, SSEE, SSEZ, SSZE and SSZZ isomers are occurred with the big change of their geometries indicated by the change of geometrical parameters (Table 2). This means that these neutral isomers must spend the large amount of energies to transform their geometries to form transition-state conformations and dissociate one proton to become the deprotonated species. On the other hand, deprotonation of the neutral SREE, SREZ, SRZE and SRZZ isomers have affected their geometries with the small change of the dihedral angles of ϕ, χ and θ.

Due to the RS/EZ geometrical isomerism, transformation among isomeric types is not possible. Then fourteen neutral HMPAO isomers, except the RREZ (RRZE) and SSEZ (SSZE), and the sixteen deprotonated species can not be transformed to the others. The geometrical patterns of the neutral and the deprotonated forms are extremely different except the SREE, SREZ, SRZE and SRZZ isomers (SR-series isomers). The geometrical parameters of the AM1 geometries of zinc(II) complexes with either the neutral or deportonated HMPAO and their Zn-N bond lengths are compared as listed in Table 3.

The Zn-N bond length searched from x-ray crystal structures of CSD using CCDC program[13] and 2009 records of zinc(II) complexes were found that the minimum, the maximum and the average Zn-N bond lengths are 1.754, 2.712 and 2.096 ± 0.092 Å, respectively. The average Zn-N bond

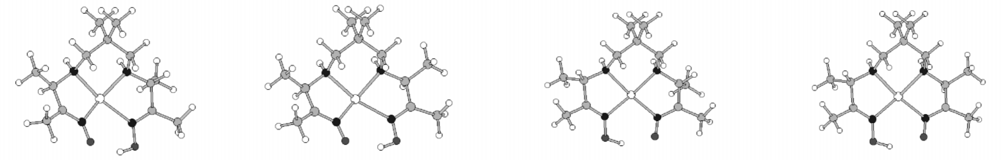


RREE/neutral
ΔE= 4.1 kcal mol$^{-1\,a}$
ΔE= 4.8 kcal mol$^{-1\,b}$

RSEE/neutral
ΔE= 4.4 kcal mol$^{-1\,a}$
ΔE= 5.3 kcal mol$^{-1\,b}$

SREE/neutral
ΔE= 0.0 kcal mol$^{-1\,a,b}$

SSEE/neutral
ΔE= 4.1 kcal mol$^{-1\,a}$
ΔE= 4.8 kcal mol$^{-1\,b}$



RREE/deprotonated
ΔE= 4.1 kcal mol$^{-1\,a}$
ΔE= 4.7 kcal mol$^{-1\,b}$

RSEE/deprotonated
ΔE= 8.5 kcal mol$^{-1\,a}$
ΔE= 9.4 kcal mol$^{-1\,b}$

SREE/deprotonated
ΔE= 0.0 kcal mol$^{-1\,a,b}$

SSEE/deprotonated
ΔE= 4.1 kcal mol$^{-1\,a}$
ΔE= 4.7 kcal mol$^{-1\,b}$

Figure 4. EE-series isomers of zinc(II) complexes with neutral and deprotonated species of HMPAO and their relative energies compared to most stable isomer (^{a}BSSE energies at HF/3-21G level and ^{b}HF/6-31G* energies without counterpoise corrections).

length found in the zinc(II) complexes with protein[14] and with dipyridine-containing macrocycles[15] are 2.1 ± 0.1 and 2.19 ± 0.06 Å, respectively. To compare the optimized geometrical bond lengths of Zn-N (Table 3) to the x-ray Zn-N bond lengths,[13-16] the complex isomers of EE-series (RREE, RSEE, SREE and SSEE) only exist. The graphical geomertries of EE isomeric type of zinc(II) complexes with the neutral and deprotonated HMPAO and their relative energies are shown in Figure 4. The HF/3-21G energies of zinc(II) complexes with neutral, deprotonated HMPAO, their related configurations and the complexations with counterpoise correction (Table 4) show that the SREE of the neutral and deprotonated forms are the most stable isomers. The SREE of Zn(II)/neutral HMPAO species is more stable than the RREE, SSEE and RSEE isomers by 4.1, 4.1 and 4.4 kcal mol^{-1} respectively and SREE of Zn(II)/deprotonated HMPAO is more stable than the RREE, SSEE and RSEE isomers by 4.4, 4.4 and 8.5 kcal mol^{-1}, respectively. Results of the HF/6-31G* energies in Table 5 show that the SREE of Zn(II)/neutral HMPAO and of Zn(II)/deprotonated HMPAO species are more stable than the RREE, SSEE and RSEE isomers by

Table 5. Total energies at HF/6-31G* theoretical level of Zn(II)/neutral and Zn(II)/deprotonated HMPAO complexes and their complexation energies without counterpoise corrections

Isomers^a	E_{ZnLH_2} ^{b}	Rel Energy^c	E_{LH_2} ^{b}	$\Delta E^0_{complex}$ ^{d}
RREE	-2653.018143700	4.8	-875.836358434	-357.5
RSEE	-2653.017345320	5.3	-875.836119613	-357.1
SREE	-2653.025783240	0.0	-875.843852113	-357.6
SSEE	-2653.018143700	4.8	-875.836358434	-357.5
Isomers^e	E_{ZnLH^-}		E_{LH^-} ^{b}	$\Delta E^1_{complex}$ ^{d}
RREE	-2652.706262490	4.7	-875.266013532	-519.7
RSEE	-2652.698779200	9.4	-875.262563661	-517.2
SREE	-2652.713807210	0.0	-875.272383724	-520.4
SSEE	-2652.706262490	4.7	-875.266013532	-519.7

^{a}neutral HMPAO, ^{b}energies in hartree, ^{c}relative energies of complexes in kcal mol^{-1}, $^d\Delta$E in kcal mol^{-1}, ^{e}deprotonated HMPAO

Table 4. Total energies at HF/3-21G theoretical level of Zn^{2+}/HMPAO (neutral and deprotonated), their counterpoise components and their complexation energies with BSSE corrections

Isomers^a	E_{ZnLH_2} ^{b}	Rel Energy ^{c}	$E_{LH_2,BSSE}$ ^{b}	$\Delta E^0_{Zn^{2+},BSSE}$ ^{b}	$\Delta E^0_{complex,BSSE}$ ^{d}
RREE	-2639.88964310	4.1	-870.97619978	-1768.33297834	-364.2
RSEE	-2639.88925173	4.4	-870.97557505	-1768.33308914	-364.3
SREE	-2639.89620806	0.0	-870.98289279	-1768.33203461	-364.8
SSEE	-2639.88964310	4.1	-870.97619978	-1768.33297834	-364.2
Isomers ^{e}	E_{ZnLH^-} ^{b}		$E_{LH^-,BSSE}$ ^{b}	$\Delta E^1_{Zn^{2+},BSSE}$ ^{b}	$\Delta E^1_{complex,BSSE}$ ^{d}
RREE	-2639.56875032	4.4	-870.42839669	-1768.33508100	-518.3
RSEE	-2639.56174676	8.5	-870.41595518	-1768.33509444	-515.4
SREE	-2639.57526067	0.0	-870.43639111	-1768.33514218	-518.6
SSEE	-2639.56875032	4.4	-870.42839669	-1768.33508100	-518.3

^{a} neutral HMPAO, ^{b} energies in hartree, ^{c} relative energies of complexes in kcal mol^{-1}, ^{d} ΔE in kcal mol^{-1}, ^{e} deprotonated HMPAO

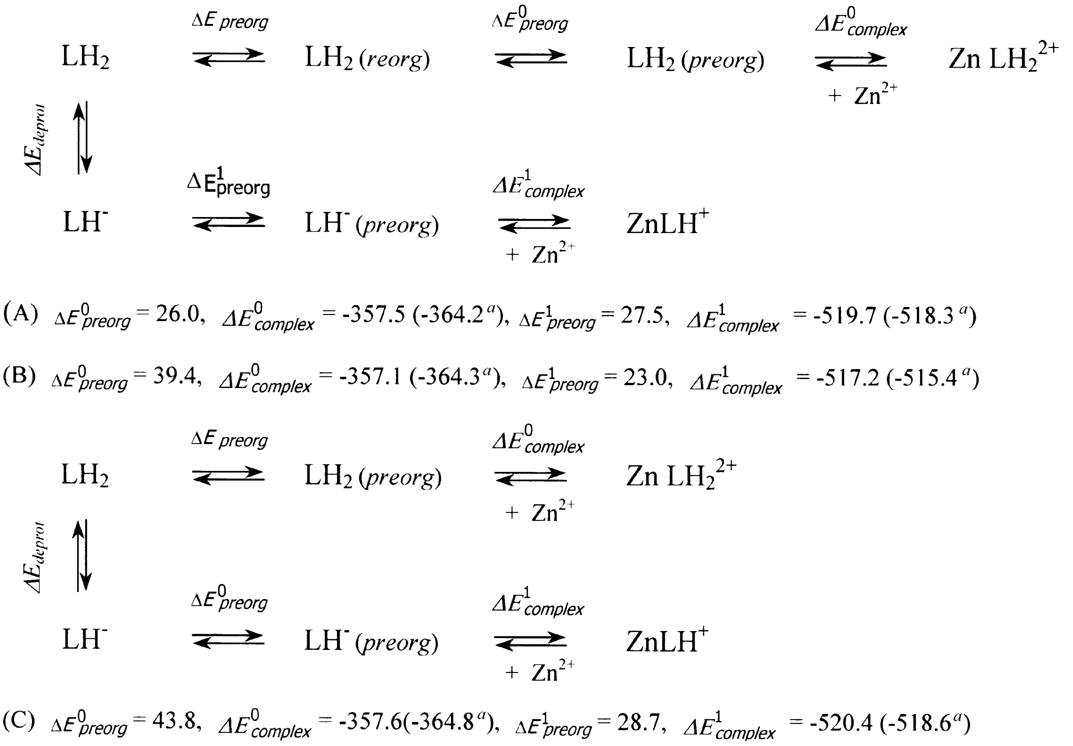
Table 6. Lowest, reorganization and pre-organization energies of neutral and deprotonated HMPAO and their relative energies

Isomers	Lowest energy[a,b]	1-Rel energy[c]	Reorganization energy[b]	2-Rel energy[d]	Pre-organization energy[b]	3-Rel energy[e]
			Neutral forms			
RREE	-875.916760553	0.0	-875.877820744	4.4	-875.836358434	4.7
RSEE	-875.909636452	4.5	-875.898981045	4.7	-875.836119613	4.9
SREE	-875.913592773	2.0	-875.913592773	0.0	-875.843852113	0.0
SSEE	-875.911144034	3.5	-875.877820744	4.4	-875.836358434	4.7
			Deprotonated forms			
RREE	-875.309789774	5.2	[f]	[g]	-875.266013532	4.0
RSEE	-875.299139717	11.9	[f]	[g]	-875.262563661	6.2
SREE	-875.318047663	0.0	[f]	[g]	-875.272383724	0.0
SSEE	-875.309789774	5.2	[f]	[g]	-875.266013532	4.0

[a]global minimum energies, [b]HF/6-31G* energies in hartree, [c]lowest energies in kcal mol^{-1}, [d]reorganized energies in kcal/mol, [e]pre-organized energies in kcal mol^{-1}, [f]the same as global minimum energies, [g]the same as 1-rel energies

respectively. Results in Table 5 and 6 show that the complexation energies of Zn(II)/HMPAO complexes derived from the HF/3-21G energies with BSSE corrections get very close to the energies computed from the HF/6-31G* energies of the corresponding types of complexes. The complexation energies at the HF/3-21G level of theory, including counterpoise corrections, of the neutral and deprotonated HMPAO get very close to their corresponding energies at the HF/6-31G* without counterpoise corrections (Table 5); they are different by 7.0 ± 0.25 and 1.6 ± 0.2 kcal mol^{-1}, respectively.

To form the Zn(II)/neutral HMPAO isomers, the neutral ligands of RREE, RSEE and SSEE isomers must be reorganized to be stable conformation and pre-organization before complexing with zinc(II) ion. According to the complexation, only four types of the RREE, RSEE, SREE and SSEE isomers either the neutral and deprotonated ligands are considered. Due to the structural reorganization of the neutral HMPAO for their complexations, the energies of their reorganized structures must be used in the comparison of their stabilities. For this reason, the SREE isomer is the most stable conformation when compare to those reorganized structures and then more stable than the RREE, RSEE and SSEE conformations by 4.4, 4.7 and 4.4 kcal mol^{-1}, respectively (Table 6). Because the EE-series isomers of deprotonated HMPAO are the same geometries of their reorganized conformations, their energies are therefore the same values; reorganized conformation is defined as a local minima geometry that will transform to be a pre-organized



(A) $\Delta E^0_{preorg} = 26.0$, $\Delta E^0_{complex} = -357.5\ (-364.2^a)$, $\Delta E^1_{preorg} = 27.5$, $\Delta E^1_{complex} = -519.7\ (-518.3^a)$

(B) $\Delta E^0_{preorg} = 39.4$, $\Delta E^0_{complex} = -357.1\ (-364.3^a)$, $\Delta E^1_{preorg} = 23.0$, $\Delta E^1_{complex} = -517.2\ (-515.4^a)$

(C) $\Delta E^0_{preorg} = 43.8$, $\Delta E^0_{complex} = -357.6(-364.8^a)$, $\Delta E^1_{preorg} = 28.7$, $\Delta E^1_{complex} = -520.4\ (-518.6^a)$

Scheme 1. Stabilization energies (kcal mol^{-1}) according to complex isomers of the (A) RREE and SSEE (B) RSEE, and (C) SREE, derived from HF/6-31G* energies. ([a]BSSE energies at HF/3-21G theoretical level, $\Delta E_{complex,BSSE}$.)

geometry for complexing with Zn(II) ion. The SREE is also the most stable isomer and more stable than the RREE, RSEE and SSEE isomers by 5.2, 11.9 and 5.2 kcal mol^{-1}, respectively.

Due to the complexations, only the RREE, RSEE, SREE and SSEE isomers of the neutral and deprotonated HMPAO are involved in reaction mechanism in terms of the stabilization energies (Scheme 1). Energies of deprotonation (ΔE_{deprot}) and reorganization (ΔE_{reorg}) of some stable conformations based on the rotational barriers of corresponding transformation process, their values have to be evaluated by consideration of energy barriers. Pre-organization energy (ΔE_{preorg}) is an energy difference between pre-organized structure according to the complexation process and stable conformation of reorganized structure.

Conclusions

We have investigated for the isomers of the neutral, deprotonated species of HMPAO and their complexes with zinc(II) ion. We found that there are twenty-two isomers (stereoisomers) of the neutral species and twenty isomers of the deprotonated species of HMPAO, respectively. The four EE-series isomers of both zinc(II) complexes with the neutral and deprotonated HMPAO have been found. Either the SREE isomers of zinc(II) complexes with the neutral and deprotonated HMPAO are the most stable isomers. Either Zn(II) complexes with the neutral or the deprotonated HMPAO, the complexes with the SREE isomers are the most stable species.

Supporting Information Materials. Listing of optimized geometrical parameters and cartesian coordinates of all proposed isomers of HMPAO is available on request from the correspondent author.

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