Reactivity of ferrocenylalkylazoles under conditions of dissociative ionization

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Electron ionization mass spectra of biologically active ferrocenylalkylazoles $CpFeC_5H_4CH(R)Az$ (R = H, Me, Et, Pr, or Ph; AzH is pyrazole, imidazole, indazole, benzoimidazole, benzotriazole, adenine, or their derivatives) were studied. The nature of the heterocyclic fragment (its ionization energy) is the main factor determining the reactivity of these compounds under conditions of dissociative electron ionization.

Key words: ferrocene, azoles, mass spectrometry, reactivity, dissociative ionization, regression analysis.

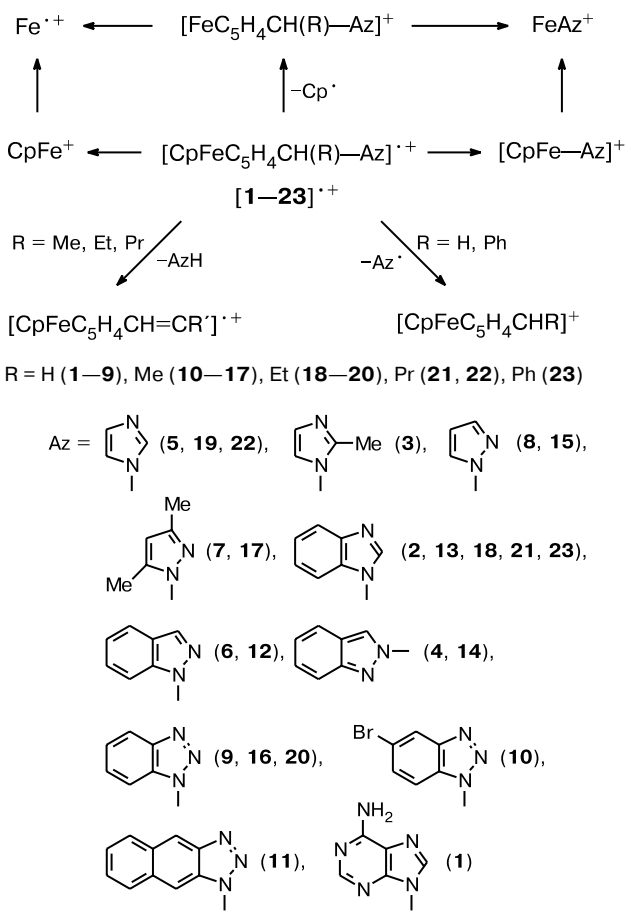
Pronounced antitumor activity of ferrocenylalkylazoles combined with low toxicity allows these compounds to be considered as precursors for the design of highly efficient drugs for chemotherapy of tumor diseases.[1—4] In this connection, studies of the physicochemical properties and reactivities of these compounds are of considerable importance. In the present study, we examined the behavior of ferrocenylalkylazoles **1—23** with the composition $CpFeC_5H_4CH(R)Az$ (R = H, Me, Et, Pr, or Ph; AzH is pyrazole, imidazole, indazole, benzoimidazole, benzotriazole, adenine, or their derivatives) under conditions of dissociative electron ionization (Scheme 1) by mass spectrometry. Our interest here is with both the analytical and research aspects of this problem. The former consists of the development of procedures for the determination of the compositions, structures, and purities of this class of biologically active compounds. The latter consists of the study of the reactivities of such molecules and their ions in the gas phase.

Results and Discussion

The mass spectra of all the compounds under study have intense peaks of molecular ions, whose fragmentation follows several paths. The ordinary cleavage of the metal—ligand bond with elimination of substituted and unsubstituted cyclopentadienyl ligands up to the formation of the free iron cation[5,6] is common to these compounds, as well as to all ferrocene derivatives.

The characteristic feature of the behavior of all ferrocenylalkylazoles under conditions of dissociative electron ionization is that they undergo a rearrangement accompanied by migration of the heterocyclic fragment to the iron atom giving rise to the $CpFeAz^+$ and $FeAz^+$ ions containing the metal—azole bond (see Scheme 1).

Scheme 1



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This process is typical of most of ferrocenylmethyl derivatives $CpFeC_5H_4CH(R)X$ containing a nucleophilic fragment (X = OH, NR_2, Hal, *etc.*).[5–7]

Another fragmentation path associated with the cleavage of the carbon—heterocycle bond substantially depends on the nature of the substituent R. If R = H or Ph, the process involves ordinary cleavage of this bond with elimination of the azolyl radical. In the case of alkyl-substituted derivatives, this process is accompanied by migration of the hydrogen atom to the heterocycle followed by elimination of the azole molecule to give ions of the corresponding vinylferrocenes and AzH^+ (see Scheme 1). An analogous rearrangement accompanied by elimination of the water molecule is characteristic also of ferrocenylalkanols $CpFeC_5H_4CH(R)OH$ (R = Me or Et).[5,7] Like the reactions of ferrocenylalkylazoles, this process occurs only with compounds containing hydrogen atoms at the β-carbon atom, *i.e.*, the rearrangement proceeds by the 1,2-elimination mechanism. This conclusion is also confirmed by the mass spectra of deuterated derivatives of ferrocenylethanol, *viz.*, $CpFeC_5H_4CD(OH)CH_3$ and $CpFeC_5H_4CD(OH)CH_2D$.[7]

Consequently, not only elimination of cyclopentadienyl ligands typical of all ferrocene derivatives, but also migration of the heterocyclic fragment to the metal atom is characteristic of the compounds under study. Depending on the nature of the substituent at the α-carbon atom, the fragmentation of the substituted cyclopentadienyl ligand accompanied by the carbon—heterocycle bond cleavage either occurs through elimination of the azolyl radical or, in the presence of the methylene group at the β position, involves migration of hydrogen with elimination of the azole molecule.

The above-described features of the process allow one to unambiguously identify ferrocenylalkylazoles based on their mass spectra. In particular, isomers **3** and **15** and isomers **7** and **19** can easily be distinguished based on m/z for the $[M - Az]^+$ (199 for compounds **3** and **7**) and $[M - HAz]^+$ (212 and 226 for compounds **15** and **19**, respectively) ions. Ferrocenylalkyl derivatives of isomeric imidazole and pyrazole (**5** and **8**) and their benzo analogs (**2** and **4** (**6**), **13** and **12** (**14**)) differ considerably in the ratio of the ion peak intensities $Z = [M - Cp]^+/[CpFe]^+$, which is always an order of magnitude larger than that observed in the spectra of pyrazole and indazole derivatives. At the same time, the mass spectra of isomers of indazole, *viz.*, isomers **4** and **6** and isomers **12** and **14**, are almost identical to each other due to isomerization of these compound.[8]

With the aim of revealing the factors responsible for the reactivity of these compounds under conditions of electron ionization, we calculated the following quantitative characteristics of the main fragmentation processes of the molecular ions of ferrocenylalkylazoles (Table 1):

Table 1. Degrees of fragmentation α_{Cp}, $\alpha_{Cp'}$, and α_{Az} and the parameters W and Z calculated from the mass spectra of ferrocenylalkylazoles $CpFeC_5H_4CH(R)Az$ (**1—23**) and the ionization potentials[10] (IP) of the corresponding azoles

Compound	α_{Cp}	$\alpha_{Cp'}$	α_{Az}	W	Z	IP /eV
1	0.71	0.52	0.39	0.17	—	7.80
2	0.33	0.45	0.65	0.19	0.05	8.00
3	0.26	0.39	0.74	0.21	—	8.50
4	0.46	0.39	0.43	0.27	2.04	8.35
5	0.32	0.40	0.64	0.27	0.30	8.81
6	0.47	0.35	0.38	0.30	2.12	8.35
7	0.49	0.19	0.26	0.31	—	9.10
8	0.45	0.21	0.22	0.33	5.35	9.25
9	0.14	0.34	0.50	0.38	—	9.20
10	0.45	0.53	0.92	0.08	—	—
11	0.29	0.41	0.90	0.10	—	—
12	0.38	0.40	0.79	0.11	0.46	8.35
13	0.23	0.33	0.76	0.14	0.01	8.00
14	0.43	0.41	0.68	0.14	0.55	8.35
15	0.39	0.29	0.46	0.19	—	9.25
16	0.24	0.32	0.74	0.22	—	9.20
17	0.41	0.22	0.40	0.26	—	—
18	0.37	0.43	0.80	0.12	—	8.00
19	0.16	0.16	0.68	0.20	—	8.81
20	0.15	0.25	0.72	0.25	—	9.20
21	0.21	0.28	0.61	0.22	—	—
22	0.14	0.23	0.56	0.27	—	—
23	0.30	0.37	0.69	0.21	—	—

— the stability of molecules against electron impact $W = I_{M^+}/\Sigma I_i$, which is a fraction of molecular ions that do not undergo fragmentation and is calculated as the ratio of the peak intensity of the molecular ion to the total ion current;

— the degrees of fragmentation with elimination of the substituted cyclopentadienyl ligands ($\alpha_{Cp'}$), the unsubstituted cyclopentadienyl ligand (α_{Cp}), and the heterocycle (α_{Az}). These parameters characterize the strengths of the metal—ligand and azole—carbon bonds and are calculated as the difference between the number of the corresponding fragments in the starting molecule and the total intensity of all ion peaks containing this fragment[9]

$$\alpha_{Cp'} = 1 - \Sigma I_{Cp'},$$
$$\alpha_{Cp} = 1 - \Sigma I_{Cp},$$
$$\alpha_{Az} = 1 - \Sigma I_{Az},$$

where $\Sigma I_{Cp'}$, ΣI_{Cp}, and ΣI_{Az} are the total intensities of the ion peaks (normalized to the total ion current) containing the Cp′, Cp, and Az fragments, respectively.

Regression analysis of these parameters for a series of ferrocenylalkylazoles **1—9** and **10—17** and the ionization potentials (IP) of the corresponding azoles[10] revealed relationships between these parameters (Table 2). In par-

Table 2. Results of regression analysis of α_{Az}, W, and IP for compounds **1—9** and **10—17**

Azoles	Equation		r	n	N
1—9	$\alpha_{Az} = -0.29IP + 2.99$	(1)	0.929	5	**3**, **5**, **9**
(R = H)	$W = 0.12IP - 0.80$	(2)	0.930	8	**6**
	$W = -0.23\alpha_{Az} + 0.38$	(3)	0.893	7	**1**, **9**
10—17	$\alpha_{Az} = -0.31IP + 3.31$	(4)	0.931	5	**16**
(R = Me)	$W = 0.11IP - 0.75$	(5)	0.866	5	**15**
	$W = -0.29\alpha_{Az} + 0.35$	(6)	0.958	8	**16**

Note: r is the correlation coefficient, n is the number of points, N are the numbers of compounds, which do not fit the equation.

ticular, the stability of these compounds against electron impact and the degree of fragmentation with elimination of the heterocycle linearly correlate with the ionization potential of the corresponding azole according to Eqs (1), (2), (4), and (5) (see Table 2). There is also a linear dependence between the W and α_{Az} parameters (Eqs (3) and (6)). As expected, a decrease in the strength of the carbon—azole bond (an increase in α_{Az}) leads to a decrease in stability of the molecular ion. For elimination of cyclopentadienyl ligands, no clear correlations with the structural or energy characteristics were found. Hence, it follows that the nature of the heterocyclic fragment (its ionization energy) is the main factor determining the reactivity of these compounds under conditions of electron ionization.

Experimental

Compounds **1**,[11] **2**, **5**, **13**, **15—19**, **21—23**,[12] **4**, **6**, **12**, **14**,[8] **3**, **7**, **8—11**, and **20** [13] were synthesized according to known procedures. All compounds were characterized by elemental analysis and ^{1}H NMR spectroscopy. The structures of compounds **1**,[14] **2**, **5**, **22**,[15] **4**, and **14** [13] were established by X-ray diffraction.

The mass spectra were obtained on a Kratos MS-890 instrument (energy of ionizing electrons was 70 eV, the temperature of the ionization chamber was 200 °C, the temperature of the evaporator of the direct inlet system was 50—100 °C) and were reduced to a monoisotopic form using the AELITA program.[16]

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