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REACTIONS OF AZINIUM CATIONS.

7.* ^{13}C NMR SPECTRA AND ELECTRON STRUCTURE OF NEUTRAL σ-ADDUCTS OF 1,4-DIAZINIUM CATIONS AND METHYLATE ANION

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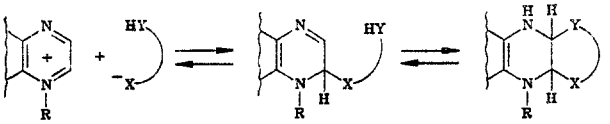
The ^{13}C NMR spectra have been recorded of a number of σ-adducts formed by pyrazinium, quinoxalinium, and pteridinium cations with methylate anion. The experimental data were compared with CNDO/2 calculations of adduct electron structure.

The important role of σ-adducts in the reactions of aromatic and heteroaromatic compounds with nucleophiles has been responsible for the increased attention that has been paid lately to these primary intermediates of nucleophilic aromatic substitution [2-7], ring closure [8, 9], cyclization [8-10], and other conversions. Reviews have been devoted to the structure, stability, and ease of formation of the anionic σ-adducts of azines [2-6]; substantially less attention has been paid to the neutral σ-adducts formed by cationic substrates of the azine series [7, 10, 11].

In a series of papers we have reported on the reactions of 1,4-diazinium cations (I) with bifunctional nucleophiles that give cyclic products (III) in which a tetrahydropyrazine ring is joined to five- and six-membered heterocycles (see reviews [10, 12, 13]).



I II III

The neutral σ-adduct II is considered the probable intermediate; this is the product of the monoaddition of a nucleophile that, however, cannot be recorded under ordinary conditions because of the rapid cyclization II → III. Such an adduct can be observed when substituents are introduced that sensitize the pyrazine system to nucleophilic attack, but only to the extent of monoaddition but not diaddition. Thus, 4-morpholino-8-ethylpteridinium salts react with anions of β-dicarbonyl compounds (acetylacetone, acetoacetic ester) to form products of addition at $C_{(7)}$ that are stable at 20°C [14]. Adducts of similar composition with 1,2-dihydropyrazine structure have been recorded in the reaction of quinoxalinium salts with β-dicarbonyl compounds, but only at lower temperatures (from −40 to −30°C) [15]. Evidently,

*For Communication 6, see [1].

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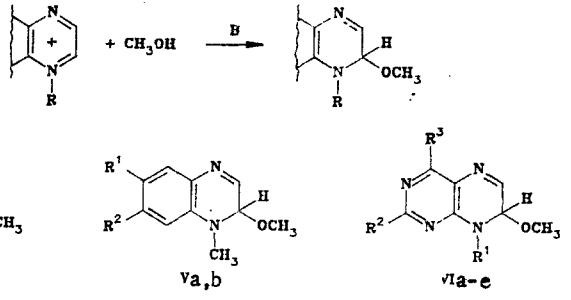
in those cases where the reaction stops at the stage of σ-adduct (II) formation, the reason should be sought in the insufficient nucleophilicity of the reagent and the low electrophilicity of the C=N bond in the dihydropyrazines II. Qualitative and quantitative data on the reactions of 1,4-diazinium cations with nucleophiles show that the activity of the C=N bond in dihydropyrazines is variable [10, 14-16]. Quinoxalinium and benzoquinoxalinium cations are most inclined to diaddition and cyclization with nucleophiles; pyrazinium cations with acceptor substituents in the ring and 4-methyl-8-alkylpteridinium salts are less reactive, while pyrazinium cation that is not ring-substituted and 4-morpholino-8-alkylpteridinium salts form neither diaddition products nor cyclic adducts [14-16].

The present work considers the problem of following the dependence of the C=N carbon electrophilicity in neutral dihydropyrazine σ-adducts on the structure of the initial pyrazinium cation. Since under identical conditions it is not possible to record the products of dinucleophile monoaddition to various diazinium cations, we chose for a study a number of σ-adducts IV-VI that were convenient and available, for observation by spectral methods. The adduct structures were varied by the introduction of substituents into the dihydropyrazine ring (IVa-c), annelation of one or two benzene rings (Va, b), joining with a pyrimidine ring, and variation of the position of the dialkylamino group (dihydropteridines VIa-e). All dihydrocompounds were obtained in methanol-D_4 solution by addition of methylate anion to the respective 1,4-diazinium cation. An exception is 1-methylbenzo[g]quinoxalinium cation, which in methanol in the presence of base forms predominantly the diaddition product [15]. For this reason the methoxy adduct Vb was obtained in chloroform by replacing the diethylamino group in the corresponding 1,2-dihydroquinoxaline by a methanol residue by the procedure of [15]. Under those conditions a mixture of mono- and dimethoxy adducts forms.

To solve the proposed question we used the dependence of ^1H and ^{13}C NMR spectral parameters on the electron structure of the molecule.



IVa-c Va,b VIa-e

IV a $R^1=CH_3$, $R^2=H$, $R^3=CONH_2$; b $R^1=CH_3$, $R^2=H$, $R^3=COOCH_3$; c $R^1=C_2H_5$, $R^2=R^3=COOCH_3$; V a $R^1=R^2=H$, b $R^1=R^2=$benzo; VI a $R^1=C_2H_5$, $R^2=H$, $R^3=$morpholino; b $R^1=CH_3$, $R^2=N(CH_3)_2$, $R^3=CH_3$; c $R^1=CH_3$, $R^2=$morpholino, $R^3=CH_3$; d $R^1=C_2H_5$, $R^2=$morpholino, $R^3=CH_3$; e $R^1=C_2H_5$, $R^2=$piperidino, $R^3=CH_3$

For this purpose we analyzed the dependence of chemical shift (CS) and spin–spin coupling constant (SSCC) on the structure of dihydro compounds IV-VI, and carried out CNDO/2 calculations for a number of model compounds.

Interpretation of the ^1H PMR spectra of dihydropyrazines IV-VI does not present any difficulties. The two characteristic doublets in the 5.3-5.6 and 7.0-7.6 ppm regions (^3J = 2.9-3.7 Hz) correspond to proton resonance at the tetragonal carbon (α-H) and the C=H bond (β-H) respectively (Table 1). We have already discussed in detail the ^1H PMR spectrum of IV-VI [16]; therefore, we note only that the CS signal changes of β-H (3-H) for IVa-c and Va, b and of 6-H for dihydropteridines VIa-e in the test compounds reach 0.6 ppm. This is evidence for the substantial effect of substituents in the pyrazine ring on the electron density at $C_{(\beta)}$. The electron density deficit is largest at $C_{(3)}$ in the dihydroquinoxaline derivatives Va, b. Then the sequence of CS changes is as follows: dihydropteridines VIa, VId, VIc, VIb, and VIe, and dihydropyrazines IVc, IVb, and IVa.

The properties of the ^{13}C NMR spectra of adducts IV-VI are shown in Tables 2 and 3. Signals have been assigned on the basis of CS and $J_{(C-H)}$ values in the proton-bonded spectra, and with consideration of the data of [17] on dihydropteridine spectra.

The signal in the 81-84 ppm region is assigned to the resonance of the tetragonal carbon in α-position to N-alkyl (Tables 2 and 3). It is well known that such a strong-field shift relative to the initial cations (60-70 ppm) is typical of changes in carbon hybridization from sp^2 to sp^3. In the ^{13}C NMR spectra without decoupling from protons, the α-carbon signal has a complex multiplicity due to interaction with α-H, β-H, and N-alkyl protons. The

TABLE 1. Chemical Shifts of α-H and β-H Protons and $^3J_{(\alpha,\beta)}$ Constants in PMR Spectra of 1,4-Diazinium Cation Adducts in CD_3OD

Compound	δ, ppm		$^3J_{(\alpha,\beta)}$, Hz
	α-H	β-H	
IVa	5,38	7,03	3,0
IVb	5,41	7,09	2,9
IVc	5,42	7,18	3,2
Va	5,32	7,60	3,2
Vb	5,32	—*	3,7
VIa	5,50	7,36	3,2
VIb	5,38	7,18	3,2
VIc	5,41	7,22	2,9
VId	5,55	7,25	3,0
VIe	5,48	7,26	2,9

*Overlapped by aromatic proton multiplet.

TABLE 2. ^{13}C NMR Spectra of Pyrazinium and Quinoxalinium Cation Adducts in CD_3OD

Compound	^{13}C CS, δ, ppm						SSCC, Hz			
	$C_{(\alpha)}(C_{(2)})$	$C_{(\beta)}(C_{(3)})$	signal of other ring carbons	R^1	R^2	R^3	$^1J_{(C_{(2)},2\text{-H})}$	$^1J_{(C_{(3)},3\text{-H})}$	$^2J_{(C_{(2)},3\text{-H})}$	$^2J_{(C_{(3)},2\text{-H})}$
IVa	82,3	138,1	136,6	41,1	—	—	169,1	187	16,5	3
IVb	82,1	139,4	115,1; 140,7	41,3	—	167,3	166	187	15	3
IVc	80,3	139,5	115,7; 141,4	16,3 48,6	165,2	167,9	165	190	16	3
Va	83,5	149,4	114,4; 119,5; 119,2; 130,9; 128,8	36,3	—	—	164	186	15,3	3
Vb*	81,6	155,6								

*In $CDCl_3$. Signals of the other atoms are not shown because a mixture of mono- and diadducts forms in solution, and it is impossible to identify aromatic carbon signals that belong to individual compounds.

values of the direct constants through a single bond, $^1J_{(C(\alpha),\alpha\text{-H})}$, lie in the 164-169 Hz range, which also corresponds to the sp^3-hybridized state of carbon. The geminal constants $^2J_{(C(\alpha),\beta\text{-H})}$ are in the 13-18 Hz range; the vicinal constants of α-carbons with N-alkyl protons are of the order of 3-6 Hz.

The β-cation signals of adducts IV-VI have also been reliably identified. In the 7,8-dihydropteridine derivatives VIa-e and 1,2-dihydropyrazine IVc the β-carbon – the only unsaturated carbon – is bonded to a proton and consequently has a direct constant $^1J_{(C(\beta),\beta\text{-H})}$. According to this feature the $C_{(\beta)}$ signal is easily divided up among the carbon signals of other C=N and C=C bonds (Tables 2 and 3). We note incidentally that $^1J_{(C(\beta),\beta\text{-H})}$ is practically unchanged for the whole IV-VI series of adducts (Tables 2 and 3). The $^1J_{(C\text{-H})}$ constants are determined, as is known [18], by the nature of carbon hybridization and the electronegativity of the neighboring atoms. Their constancy in the σ-adduct series IV-VI is evidence that this series indeed contains a dihydropyrazine segment that is constant in geometry and nature of bonds; consequently the differences in the ^{13}C CS of $C_{(\beta)}$ are related to mesomeric effects of substituents. In the ^{13}C NMR spectra of the methoxyl adducts of pyrazinium cations IVa, b the direct constants $^1J_{(C\text{-H})}$ have the signals of the two methine carbons $C_{(3)}$ and $C_{(6)}$. But is easy to differentiate them by multiplicity in the proton-related ^{13}C NMR spectra. The reason is that the $C_{(3)}$ ($C_{(\beta)}$) signal appears as a doublet of doublets, due to interaction with 3-H and 2-H (α-H) protons, whereas the $C_{(6)}$ signal appears as a doublet of quartets due to interaction with the 6-H and N-methyl protons. In 1,2-dihydroquinoxaline Va the β-carbon signal is easily distinguished from the benzene ring carbon signals by two features. First, the signals of the methine carbons of the benzene ring have a more complex multiplicity than the $C_{(\beta)}$ signal, due to interaction with the protons of the

TABLE 3. ^{13}C NMR Spectra of Pteridinium Cation Adducts in CD_3OD

Compound	^{13}C CS, δ, ppm						SSCC, Hz			
	$C_{(\alpha)}(C_{(7)})$	$C_{(\beta)}(C_{(6)})$	signals of other ring carbons	R^1	R^2	R^3	$^1J_{(C_{(6)},6\text{-H})}$	$^1J_{(C_{(7)},7\text{-H})}$	$^2J_{(C_{(7)},6\text{-H})}$	$^2J_{(C_{(6)},7\text{-H})}$
VIa	82,3	143,2	153,4; 156,1; 159,9; 111,6	45,3 15,5	—	49,5	188,6	164	15	4
VIb	84,3	143,5	115,6; 154,2; 161,2; 163,8	32,6	37,4	19,1	—	—	—	—
VIc	84.2	144,3	116,3; 154,3; 160,5; 163,9	32,7	45,5 67,7	19,2	187	168,5	15	3
VId	82,9	144,5	116,3; 153,9; 160,5; 164,2	13,6 41,7	45,6	19,3	187	161	18	4
VIe	83,0	143,6	115,6; 153,9; 160,4; 164,1	13,6 41,7	25,8 26,6 26,8 46,0	19,2	187	167	13	3

neighboring atoms. Furthermore, the value of direct SSCC for the resonance of the methine carbons of the benzene ring, $^1J_{(C\text{-}H)}$ = 158-160 Hz, differs significantly from $^1J_{(C(\beta),\beta\text{-}H)}$ = 186 Hz.

The signals of the other carbons in the ^{13}C NMR spectra of compounds IV-VI were assigned on the basis of the data of [18, 19] according to the CS for compounds for similar structure.

From analysis of the dependence of the ^{13}C NMR spectral parameters of adducts IV-VI on structure, the following conclusions can be drawn.

(1) The chemical shifts of the α-carbons and the values of the $^1J_{(C(\alpha),\alpha\text{-}H)}$ constants remain practically constant when the substituents in the dihydropyrazine ring are varied.

(2) Most sensitive to structural changes in 1,4-diazinium salts is the location of the β-carbon signal, the chemical shifts of which in IV-VI lie in the 138-155 ppm range.

The constancy of the dihydropyrazine segment and the absence of steric effects – of similarly oriented anisotropic groups, of "heavy" atoms, of induced electrical fields – all permit us to conclude that the main contribution to the change in C=N carbon shielding constants comes from the mesomeric effects of the substituents transmitted through the unsaturated molecular shells. The shielding of the ^{13}C nuclei is linearly related to the electron density at the atoms; consequently, the CS of the C=N carbon can be considered as a criterion of electron density deficit [18]. Using this parameter we can divide our test compounds into three groups. The first group is the pyrazinium cations, the methoxy adducts of which have a $C_{(\beta)}$ CS of 138-139 ppm; i.e., they are the most shielded of the test dihydropyrazines. In fact the monocyclic pyrazinium cations have the least tendency to take part in nucleophile diaddition, including cyclization with dinucleophiles [10, 16]. The second group is the pteridinium salts, which are moderately reactive in diaddition and cyclization. The $C_{(\beta)}$ of their methoxy adducts appear in the 143-145 ppm region. Finally, the third group, the most reactive in nucleophile diaddition, are the quinoxalinium and benzoquinoxalinium salts, the methoxy adducts of which, Va, b, have $C_{(\beta)}$ CS of 149.4 and 155.6 ppm, respectively (Table 2).

The differences in $C_{(\beta)}$ CS among dihydropyrazines, quinoxalines, and pteridines are related to the electron effects of the substituents on the pyrazine ring. Therefore, to determine the electron structure of the adducts theoretical calculations were carried out for a series of model compounds, A-D, by the CNDO/2 method. To simplify the calculations certain structural changes were introduced that would not substantially affect the electron structure of the molecules: methoxyl at the tetragonal carbon was replaced by hydroxyl, morpholine substituent was replaced by dimethylamino, and N-ethyl was replaced by N-methyl.

The electron structures of the molecules are shown in the diagrams of Fig. 1. Charges on atoms and resonance energies of individual bonds are shown.

The calculations show that $C_{(\beta)}$ in dihydroquinoxaline C carries a larger positive charge than in dihydropyrazines A and B or dihydropteridines D and E. According to the positive

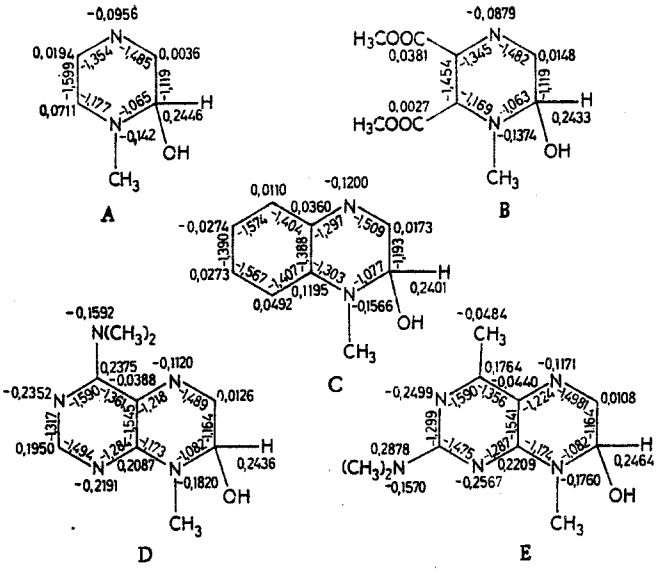


Fig. 1. Charge distribution on atoms (in electron charge units) and resonance energy of bonds (in atomic units) in 1,2-dihydropyrazines (A, B), 1,2-dihydroquinoxaline (C), and 7,8-dihydropteridines (D, E).

charge at $C_{(\beta)}$, compounds A-E line up in the following order: C > B > D > E > A (Fig. 1). The sequence of $C_{(\beta)}$ CS changes in the actual spectra, Va > VIa-e > IVc, does not entirely agree with this sequence, but for dihydroquinoxaline Va the calculated data are close to the experimental. The other calculated parameter, viz., the C=N bond resonance energy, also has its maximum value in dihydroquinoxaline C; this indicates that this bond is more localized than in other adducts, and is therefore more reactive. The absolute values of C=N bond resonance energy decreases in the following order: dihydroquinoxaline C, dihydropteridines E and D, dihydropyrazines A and B. Just as in the ^1H and ^{13}C NMR spectra of methoxy adducts, the calculated data indicate an increased electrophilicity of the $C_{(3)}$ position in quinoxalinium adducts Va, b over that of other diazines; this explains the greater tendency of quinoxalines to react by diaddition and cyclization with dinucleophiles. The calculated data also explain the low reactivity of unsubstituted pyrazinium cation, which does not undergo cyclization with dinucleophiles. The diagram of compound A shows that the charge on the β-carbon, $C_{(3)}$, is lower than on $C_{(6)}$, almost an order of magnitude lower than in benzo- and pyrimido-annelated dihydropyrazines; this explains the low tendency of unsubstituted dihydropyrazine to undergo secondary addition of nucleophiles.

Our data show that both the ^1H and ^{13}C NMR spectral parameters and the quantum chemical calculations for methoxy adducts can be used to predict the reactivity of 1,-4-diazinium cations.

EXPERIMENTAL

Quantum chemical calculations in a CNDO/2 approximation [20] were carried out with a program modified to fit an EC-1022 computer [21] using "averaged" molecular geometry. Energy distribution was carried out by the procedure of [22]. ^1H and ^{13}C NMR spectra were obtained with Bruker WP-80 [20.13 (^{13}C) and 80.13 (^1H) MHz] instruments. To increase sensitivity in obtaining ^{13}C NMR spectra, the DEPT pulse sequence was used [23].

Recording of ^1H and ^{13}C NMR Spectra of Methoxy Adducts IVa-c, Va, VIa-e. To a weighed sample of 1,4-diazine [16] (~0.1 mmole) suspended in 2 ml of methanol-D_4 was added 10 ml (0.1 mmole) of triethylamine by means of a graduated capillary. The quaternary salt dissolved completely. The solution was transferred to a 10-mm ampul of the NMR spectrometer, TMS was added and the ^1H and ^{13}C NMR spectra of the adduct were recorded at 27°C. Under these conditions the adducts are stable for many hours, and no appreciable amounts of diadduct or products of other structure form. The quinoxalinium cation is an exception; at 27°C it forms, along with monoadduct Va, comparable amounts of dimethoxy adduct [11], but the signals can easily be distinguished in the spectra.

Methoxy Adduct Vb. The product of diethylamine addition to N-methylbenzoquinoxalinium cation, obtained according to [15], was dissolved in 2 ml of $CDCl_3$, and the equivalent amount of methanol-D_4 was added. A 3:1 mixture of mono- and diadduct formed.

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