ARE 1,4-DIHYDROPYRAZINES ANTIAROMATIC? *Ab initio* STUDY OF 1,4-DIHYDROPYRAZINES AND THEIR TETRAHYDRO DERIVATIVES

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A set of twenty molecules containing 1,4-dihydro- or tetrahydropyrazine ring was calculated using *ab initio* methods. This set also includes previously prepared diacetyl- or disilyl-dihydropyrazines. Structures of 1,4-dihydropyrazine derivatives are strongly dependent on ring substituents and change from planar to heavily distorted boat conformations. In the planar and near-planar structures of some 1,4-diacyl- or 1,4-diformyl-1,4-dihydropyrazines, conjugation of nitrogen lone pairs and ring bond π electrons is small. Structures, bond lengths and bond orders of 1,4-dihydropyrazines and their tetrahydro derivatives are similar. The isodesmic energy shows tendency rather to aromatic then to antiaromatic conjugation. On the basis of structural, electronic and energy arguments it is proposed to classify 1,4-dihydropyrazines as nonaromatic compounds.

Key words: Antiaromaticity; Aromaticity; Pyrazines; DFT calculations; *Ab initio* calculations; Isodesmic energy.

Hückel's rule[1–5] predicts the existence of two types of cyclic unsaturated molecules – aromatic type with $4n + 2$ π electrons in conjugation, with great stability due to the resonance effect of these electrons, and antiaromatic type with $4n$ π electrons, destabilized due to the opposite effect. Between these two extremes there is a class of nonaromatic compounds. Carbocyclic compounds with $4n$ π electrons exhibit the purest antiaromatic character. The presence of a heteroatom decreases the antiaromatic character[6]. It was supposed that derivatives of 1,4-dihydropyrazines (and related 1,4-dihydroquinoxalines and 5,10-dihydrophenazines) might be a convenient candidate for antiaromatic compounds[7–16] because their four nitrogen lone-pair electrons which in conjugation with four π electrons of C=C double bonds form an 8 π-electron system.

The most direct criterion of antiaromaticity is the relative stability of studied compounds, obtained by the calorimetric measurement of their heats of formation and other thermodynamic parameters[17]. Often used in the study of antiaromaticity is the multistep one-electron reduction and oxidation by cyclic voltammetry. This method compares the stability of dianions and dications of antiaromatic compounds with that of their aromatic dianion or dication counterparts[6,18,19]. An indirect criterion for antiaromaticity is based on NMR spectroscopy[6,9]. The $4n$-π anulenes exhibit down-field shift of inner protons and a high-field shift of outer protons. This paratropic effect is typical of antiaromatic compounds, in contrast to aromatic ones showing the reverse (diatropic) effect. Another NMR method used for antiaromatic compounds is charge density determination[20]. The other methods, such as X-ray difraction[9–16], UV-VIS spectroscopy[21] or electron spin resonance in combination with ENDOR techniques[22], are less powerful for study of antiaromaticity.

It is a question whether we can determine the antiaromatic character from theoretically predicted structures. The systems try to avoid the unstable electronic structure of a planar antiaromatic system by a geometrical distortion, which breaks down the overlap of p orbitals contributing to the π system. A conformational criterion was suggested for classification of aromaticity of six-membered rings[23,24]. According to this criterion, aromatic rings are planar in their optimum structures whereas antiaromatic rings are nonplanar. Houk and coworkers[24] suggested classifying molecules with a small energy difference between planar and nonplanar structures of their π-electron rings as nonaromatic. According to this criterion the 1,4-dihydropyrazines are nonaromatic. Murray and coworkers[25] nevertheless classified these compounds as antiaromatic. An interesting comparison results from calculations of parent pyrazine and quinoxaline compounds[26–27] or of three-membered heterocycles, some of which are classified as antiaromatic[28–31].

The 1,4-dihydropyrazine ring is an essential part of biochemically important molecules, such as 1,5-dihydroflavins[32–35] and certain luciferins[36,37]. It is supposed to be an intermediate in Shiff base-mediated crosslinking in the living body[38] and it has found application in the photographic process of silver colour bleaching[39]. Until now only a few 1,4-dihydropyrazine derivatives have been known because of their low stability. One of their typical reactions is rearrangement to 1,2-dihydropyrazines[40,41]. The parent 1,4-dihydropyrazine has not yet been synthesized. The 1,4-dialkyl-2,6-diaryl-1,4-dihydropyrazines, systematically studied in the seventies[40–43], adopt a strongly nonplanar boat conformation, which does not allow π conjuga-

tion. An extension of the conjugated system, such as in 5,10-dihydrophenazines, increases stability and allowed synthesis of *N*,*N*′-dimethyl or diphenyl derivatives[44]. The simplest studied system containing 1,4-dihydropyrazine-like subsystem unsubstituted on the nitrogen atom is 2,3-diphenylquinoxaline dianion[45]. The largest studied compounds, isoelectronic with 1,4-dihydropyrazine, were the pyrazines containing dianions[6] of conjugated systems having up to seven rings. The quoted paper[6] is also an excellent review of progress in the study of antiaromatic compounds prepared until 1988. The idea to remove electrons from the pyrazine ring and to decrease the destabilizing antiaromatic effect led to synthesis of several *N*,*N*′-diacyl-1,4-dihydropyrazines[7,8,46]. From this point of view the luciferins are also formally *N*-monoacyl derivatives, dihydroflavins are formally *C*-monoacyl derivatives and recently published 4a,8a-diaza-2,6-dioxa-3,4,7,8-tetramethylanthracene-1,5-dione[47] is formally a diacyl derivative. The largest class of synthesized 1,4-dihydropyrazines is *N*,*N*′-disilyl derivatives intensively studied by Kaim[9–16]. The experimentally found properties of these compounds can be explained in terms of antiaromaticity.

Due to difficult synthesis and growing importance of the study of 1,4-dihydropyrazines, it is useful to predict the structure of these compounds theoretically using methods of quantum chemistry. First attempts were performed using semiempirical MNDO calculations[10] (recently supplemented by INDO/S study of radical cations[16]). The progress in computer technique allows us to perform *ab initio* calculations using reliable basis sets for the smallest, yet unknown, 1,4-dihydropyrazine derivatives. There exist only two above mentioned recent publications[23,25] dealing with the *ab initio* calculations of 1,4-dihydropyrazines. In the first[23] publication, Hartree–Fock calculations with the 3-21G basis set are used, while another study[25] is performed at the MP2/6-31G*//HF/3-21G level of sophistication.

The aim of this work is to discuss the possible antiaromaticity of the wide range of 1,4-diacetyl-1,4-dihydropyrazines and some related compounds on the basis of *ab initio* calculations.

METHODS

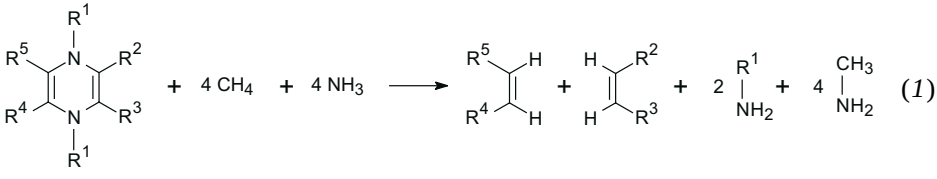
The theoretical investigation has been carried out using *ab initio* quantum-chemical methods. Geometrical optimizations were performed at the DFT (B3LYP) level using a 6-31G* basis set. The initial geometry was selected asymmetrical with *N*-substituents almost perpendicular to the pyrazine ring

to allow maximum freedom for optimization. The computations were carried out using the Gaussian 98 program package[48].

We tested the quality of the DFT results using structures **1**, **1′**, **2**, and 1,2,3,4-tetrahydropyrazine. The B3LYP method, using the same 6-31G* basis set, predicts practically identical geometries as MP2/6-31G* (maximum deviations: 0.2 pm for bond lengths; 0.5° for bond angles and 3° for nonplanarity angles, see Fig. 2). The geometries predicted at lower level (HF/3-21G) have reasonable bond lengths and angles (typical deviations 2 pm and 3°), but the pyramidal nitrogen is much too flattened.

The isodesmic energy does not depend very much on the used geometry (5 kJ mol^{-1} difference between HF, MP2, and DFT geometries) due to the error compensation. The MP2 isodesmic energies, comparing to CCSD(T)/6-31G* ones, are too low (**1**, **1′**: 18 kJ mol^{-1}; **2**: 29 kJ mol^{-1}; tetrahydropyrazine: 16 kJ mol^{-1}). The B3LYP method gives, however, an excellent agreement with the CCSD(T) results, within 1.5 kJ mol^{-1} for the compounds used for testing. Therefore we have selected the B3LYP/6-31G* method for both the optimization and energy calculations.

The isodesmic energy calculation was used to determine stability of the compounds, as it was used for the first time by Murray and coworkers[25] for the *ab initio* calculations of antiaromatic compounds. In the present paper the pyrazine ring, which appears in isodesmic reactions, was replaced by simple acyclic compounds (Eq. (*1*)).



(*1*)

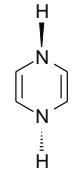
RESULTS

A list of twenty molecules calculated in the present paper is shown in Scheme 1. The selected optimized geometrical parameters are given in Table I (bond lengths) and Table II (bond angles and nonplanarity angles). The definition of these parameters is illustrated in Figs 1 and 2. The nondiagonal elements of the Mulliken population analysis matrix corresponding to selected bonds are also given in the Table I.

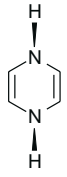
Molecular energies calculated at the B3LYP/6-31G* level are presented in Table III. The second column of Table III shows the isodesmic energies of calculated molecules evaluated at the same level. The last column of this ta-

ble gives the difference between the isodesmic energies of individual compounds and the parent system (compound **1**).

The previous results[23,25] obtained for 1,4-dihydropyrazine **1′** are completed by calculations of its chair conformer **1**. Planar structures were found for 1,4-diformyl-1,4-dihydropyrazine **2** and 1,4-diacetyl-1,4-dihydropyrazines **3a** and **3a′** (even if optimization was started from nonplanar



1



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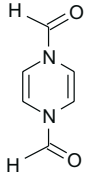

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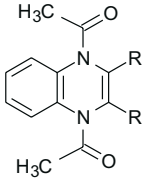
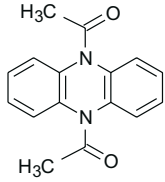


4a, R = H
4b, R = CH_3



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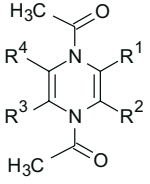
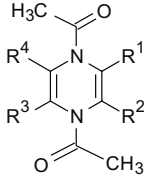
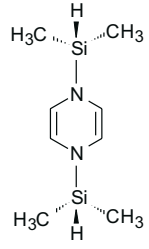


3a, R^1= R^2= R^3= R^4= H
3b, R^1= CH_3
R^2= R^3= R^4= H
3c, R^1= R^3= CH_3
R^2= R^4= H
3d, R^1= R^2= CH_3
R^3= R^4= H



3a', R^1= R^2= R^3= R^4= H
3b', R^1= CH_3
R^2= R^3= R^4= H
3c', R^1= R^3= CH_3
R^2= R^4= H



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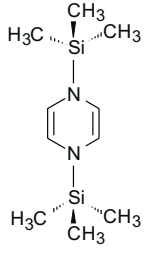

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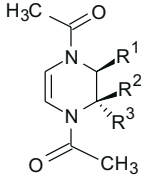
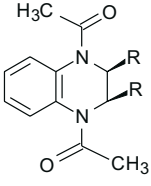


8a, R^1= R^2= R^3= H
8b, R^1= R^3= CH_3
R^2= H
8b', R^1= R^2= CH_3
R^3= H



9a, R = H
9b, R = CH_3

Calculated 1,4-dihydro- and 1,2,3,4-tetrahydropyrazine structures

SCHEME 1

TABLE I

Selected bond lengths r (see Fig. 1) in various pyrazine structures obtained by B3LYP/6-31G* optimization and nondiagonal Mulliken matrix elements corresponding to the respective bonds (bond orders p)

Structure	C=C or C–C bonds		N–C bonds		N–R bonds	
	r_1 or r_2[a], pm	p	r_3 and r_4, pm	p	r_5[b], pm	p
1	133.7	0.682	142.6	0.296	101.8	0.317
1′	133.6	0.690	142.7	0.293	101.8	0.306
2	133.5	0.574	141.6	0.240	137.9	0.239
	133.6	0.632	141.0	0.269		
3a	133.4	0.547	141.9	0.249	139.2	0.244
	134.0	0.635	141.0	0.274		
3a′	133.7	0.589	141.4	0.262	139.2	0.249
	133.7	0.589	141.5	0.261		
3b	134.1	0.593	144.3	0.277	139.4	0.244
	133.7	0.636	141.8	0.250		
3b′	134.3	0.589	143.7	0.261	139.4	0.244
	133.5	0.637	142.4	0.265		
3c	133.8	0.609	144.0	0.260	139.3	0.241
	134.3	0.636	141.6	0.268		
3c′	134.0	0.636	143.3	0.270	139.3	0.241
	134.0	0.636	142.2	0.253		
3d	134.9	0.641	144.4	0.240	139.4	0.239
	133.5	0.634	141.5	0.296		
4a	133.2	0.596	142.4	0.262	140.0	0.247
	141.3	0.495	142.3	0.211		
4b	134.5	0.663	145.0	0.230	139.8	0.232
	140.5	0.510	142.5	0.217		
5	140.5	0.501	143.7	0.199	140.2	0.243
	140.6	0.504	142.5	0.214		
6	133.8	0.668	142.5	0.285	175.9	0.371
7	133.8	0.665	142.5	0.291	176.4	0.363
8a	153.3	0.336	146.1	0.283	138.6	0.253
	134.4	0.589	140.6	0.283		
8b	154.8	0.327	147.2	0.268	138.5	0.256
	134.4	0.585	140.6	0.277		
8b′	155.7	0.343	146.6	0.271	138.3	0.257
	134.1	0.584	140.2	0.276		
9a	152.1	0.364	145.9	0.276	138.9	0.253
	141.6	0.487	142.1	0.203		
9b	156.7	0.353	147.2	0.278	138.6	0.254
	140.7	0.499	142.0	0.207		

[a] For comparison: ethylene d_{CC} = 133.1; 2-butene d_{CC} = 133.8; ethane d_{CC} = 153.0; butane d_{CC} = 153.4; benzene d_{CC} = 139.6 pm. B3LYP/6-31G* results. [b] $OHC–NH_2$ d_{CN} = 136.3; $O(CH_3)C–NH_2$ d_{CN} = 137.0 pm. Data calculated by the same procedure.

TABLE II

Calculated angles (in degrees; see Fig. 2) of various pyrazine structures. The angle $\tau(C_iC_jC_kC_l)$ shows deviation of pyrazine C=C (C–C) bonds from planarity. C_a represents the *N*-substituent carbon atom (equivalent to Si in silyl substituted systems or H in the parent system). Only $\alpha(NX_1X_2)$ [$\alpha(C_aX_1X_2)$] angle is presented if it is identical to $\alpha(N'X_2X_1)$ [$\alpha(C'_aX_2X_1)$] (which implies a boat conformation)

Structure	$\tau(C_iC_jC_kC_l)$	$\alpha(NX_1X_2)$ $\alpha(N'X_2X_1)$	$\alpha(C_aX_1X_2)$ $\alpha(C'_aX_2X_1)$	$\tau(C_iNC_aO)$ $\tau(C_kN'C'_aO')$
1	0	176 184	204 156	–
1′	0	170	196	–
2	0	180	180	0
3a	0	180 180	178 182	0
3a′	0	180	178	0
3b	0	163 166	158 169	0 3
3b′	0	162 165	158 169	0 2
3c	0	156 156	154 156	0 7
3c′	0	156	154	0
3d	0	153	150	±1
4a	0	153	153	±9
4b	0	144	137	±7
5	0	146	142	±12
6	0	166	157	–
7	0	166	159	–
8a	15	153 295	154 201	1 4
8b	16	153 207	155 204	1 2
8b′	16	151 204	153 200	0 13
9a	14	134 187	123 189	10 2
9b	8	131 150	128 146	6 9

structures). Condensation of other cycles to the parent molecule has only small influence on the pyrazine ring structure, as demonstrated by the structure of 1,4-diacetyl-1,4-dihydroquinoxaline **4a**, 1,4-diacetyl-2,3-dimethyl-1,4-dihydroquinoxaline **4b**, and 5,10-diacetyl-5,10-dihydrophenazine **5**.

One or two methyl substituents on the pyrazine ring cause nonplanarity of the ring, which increases in the following sequence: 1,4-diacetyl-1,4-dihydro-2-methylpyrazines **3b**, **3b′** < 1,4-diacetyl-2,5-dimethyl-1,4-dihydropyrazines **3c**, **3c′** < 1,4-diacetyl-2,3-dimethyl-1,4-dihydropyrazine **3d** < 1,4-diacetyl-2,3-dimethyl-1,4-dihydroquinoxaline **4b**. Selected nonplanar structures are depicted in Fig. 3.

1,4-Bis(dimethylsilyl)-1,4-dihydropyrazine **6** and its 1,4-bis(trimethylsilyl) analogue **7** are examples of already synthesized silyl substituted 1,4-dihydropyrazines[9–16]. Their calculated structures adopt rather flat boat conformations.

Compounds **8** and **9** have tetrahydropyrazine ring instead of conjugated dihydropyrazine systems. The longer C–C single bond of 1,4-diacetyl-1,2,3,4-tetrahydropyrazine **8a** and 1,4-diacetyl-2,3-dimethyl-1,2,3,4-tetrahydropyrazines **8b** and **8b′** causes chair conformations; however, the deviation of the other atoms from planarity is relatively small. Both 1,4-di-

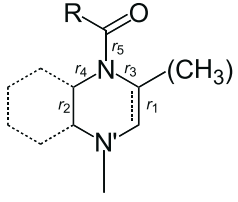


FIG. 1
Definition of selected bonds used in Table I. The calculated molecules are oriented with the top acetyl or formyl oxygen (if applicable) to the right, close to the methyl group or single bond (if any). This orientation corresponds to the Scheme 1

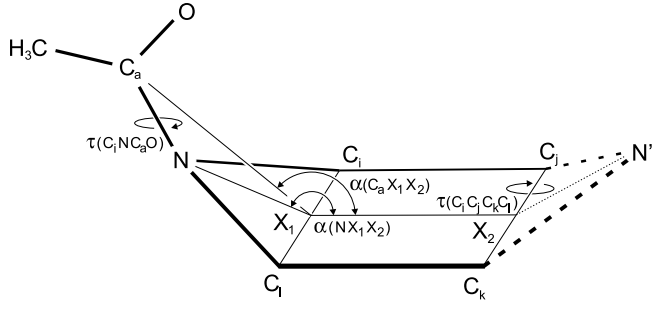


FIG. 2
Definition of selected angles used in Table II

acetyl-1,2,3,4-tetrahydroquinoxaline **9a** and 1,4-diacetyl-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline **9b** adopt a boat conformation similar to the **4b** structure (see Fig. 3).

DISCUSSION

Comparison with X-Ray Structures

The calculated structures of disilyl substituted compounds **6** and **7** are in good agreement (deviations: $\alpha_{SiNC} < 2°$; $\alpha_{CNC} < 1°$; $\alpha_{NCC} < 1°$; $d_{SiN} < 2$ pm;

TABLE III
Calculated B3LYP/6-31G* energies of various pyrazine structures

Structure	Total energy hartree	Isodesmic energy[a] kJ mol^{-1}	Relative isodemic energy[b] kJ mol^{-1}
1	–265.475442	–150.0	0
1′	–265.475377	–149.8	0.2
2	–492.172406	–189.8	–39.8
3a	–570.814309	–178.0	–28.0
3a′	–570.815202	–179.5	–29.5
3b	–610.127108	–158.0	–8.0
3b′	–610.128058	–160.5	–10.5
3c	–649.439244	–137.1	12.9
3c′	–649.443269	–147.7	2.3
3d	–649.437230	–139.4	10.6
4a	–724.457209	–129.1	20.9
4b	–803.088514	–113.4	36.6
5	–878.108928	–104.2	45.8
6	–1 004.215582	–145.5	4.4
7	–1 082.872062	–146.1	3.9
8a	–572.043460	–140.9	9.1
8b	–650.675342	–152.1	–2.1
8b′	–650.662617	–118.7	31.3
9a	–725.684934	–89.1	60.9
9b	–804.309577	–81.3	68.7

[a] Computed according to Eq. (*1*). [b] Isodesmic energy relative to the parent compound **1**.

$d_{NC} < 1$ pm; $d_{CC} < 1$ pm) with the corresponding X-ray structural parameters of the flat boat 2,3,5,6-tetramethyl-1,4-bis(trimethylsilyl) (ref.[11]), 2,3,5,6-tetramethyl-1,4-bis(triisopropylsilyl) (ref.[12]), and 2,5-dimethyl-1,4-bis(triisopropylsilyl) (ref.[13]) analogues. In contrast to the calculated results, the X-ray structures of the 1,4-bis(triisopropyl)silyl-1,4-dihydropyrazine[12] and compound **7** (ref.[11]) are planar. For these planar systems, the differences in bond lengths also lie in the above-mentioned limits. The planarity is probably due to the crystal packing forces. The energy difference between planar and nonplanar structures is usually small[23] (12.1 and 0.5 kJ mol^{-1}, respectively, for the corresponding dianions) and these molecules form stacking complexes which force planar conformations in the absence of ring substituents. The methyl substituted systems prefer butterfly structures which allow nonplanar conformations of *N*-substituents (see Table IV for a comparison of calculated and X-ray structures).

There exist two conformers with acetyl (formyl) groups in mutual *cis* and *trans* orientation of all the studied *N*,*N*′-diacetyl (-diformyl) compounds, as was shown experimentally by NMR measurements[8]. The energy difference between these two conformers is not high, as demonstrated in Table III for

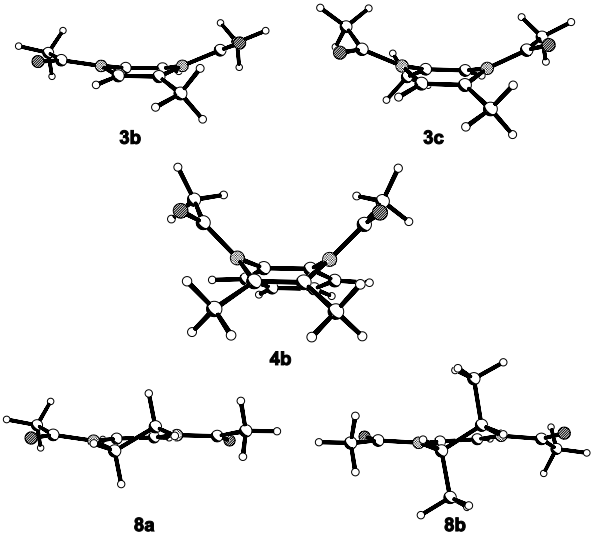


FIG. 3
Optimized structures (B3LYP/6-31G*) of selected 1,4-dihydropyrazines (**3b**, **3c**, and **4b**) with different nonplanarity of the boat conformation and 1,2,3,4-tetrahydropyrazines (**8a**, **8b**) in chair conformation

compounds **3a**, **3a′**, **3b**, **3b′** (≈2 kJ mol^{-1}) and **3c**, **3c′** (10 kJ mol^{-1} due to the methyl–methyl repulsion). Therefore we have limited ourselves to computation of only one of the conformers of the remaining compounds.

Influence of N-Substituents

The angle between the N–H bond and the ring plane of compounds **1** and **1′** shows the predominantly pyramidal character of nitrogen atoms. This fact together with short C=C bond lengths (133.7 and 133.6 pm, respectively) suggests that parent 1,4-dihydropyrazine exhibits only small cyclic conjugation. The formyl or acetyl substituents change the situation. The nitrogen atom becomes planar and therefore its valence orbitals are sp^2-hybridized in *N*-acetylated and *N*-formylated 1,4-dihydropyrazines. This allows conjugation of the nitrogen lone pair with the C=O bond of the substituent. Despite of the planarity of the ring, the conjugation with the ring C=C bond does not occur because the C=C bond length and bond or-

TABLE IV
Comparison of the calculated bond lengths of silylated dihydropyrazines with those obtained by X-ray diffraction

Structure			Bond length, pm			Source
N substituent	C substituent	ring conf.	C=C	N–C	Si–N	
Me_2HSi	–	boat	133.8	142.5	175.9	this paper[a]
Me_3Si	–	boat	133.8	142.5	176.4	this paper[b]
Me_3Si	–	planar	132.4	141.6–142.1	174.5	X-ray[11]
i-Pr_3Si	–	planar	133.0	141.4–141.6	174.0	X-ray[12]
t-BuMe_2Si	Me	boat	133.4–132.7	143.7–144.6	175.5–175.8	X-ray[13]
t-BuMe_2Si	2,3-(–CH=CH–CH=CH–)	boat	131.9–141.6	142.0–142.3	176.1	X-ray[14]
i-Pr_3Si	2,5-Me	boat	132.7–133.0	142.9–143.2	175.2–175.6	X-ray[15]
Me_3Si	Me	boat	133.1–132.2	143.9–144.5	174.4–175.4	X-ray[11]

[a] Compound **6**. [b] Compound **7**.

der correspond rather to an isolated double bond and not to a conjugated one.

Influence of Ring Substituents

Due to the steric repulsion between the methyl substituents and the hydrogen atoms of acetyl groups, the pyrazine ring exhibits a boat conformation in structures **3b**, **3b′**, **3c**, **3c′**, **3d**, and **4b**. If the acetyl group is oriented with its oxygen atom toward the methyl group, the repulsion force between oxygen lone pairs and methyl substituents is large enough to force the formation of a flat boat conformation. In the monomethylated structures **3b** and **3b′**, nitrogen atoms and acetyl groups are only little deviated from the C=C bond plane, but the deviation is growing with increasing steric repulsion in **3c**, **3c′**, and **3d** (Fig. 3). Because the nitrogen atoms are still planar, the π conjugation between C=O π bonds and nitrogen lone pairs is probably not completely disrupted. However, the conjugation is not strong enough to form a rotational barrier for the acetyl group, like in compounds **3a** and **3a′**, as it is seen from a comparison of experimental NMR data[8,46] for **4b** and **3a**, **3a′**. The C=C bonds are still parallel, their lengths and bond orders corresponding again to the isolated double bond.

In contrast to methyl substituents, the condensation of other π rings to the parent molecule preserves the planar structure. The predicted C=C bond is longer than in the original system, which is in a good agreement with the structure of quinoxaline[27]. Because of the steric repulsion between acetyl groups and benzene ring hydrogens, the acetyls are partially tilted from the ideal position and rotated from the quinoxaline plane (see Fig. 4 and Table I).

Bond Orders and Charge Distribution

The following conclusions can be drawn from the bond orders of the Mulliken population analysis:

– Bond orders of the C=C bonds correspond to the strongly isolated double bonds, as results from the comparison of their values with the bond order in ethylene (0.687). Exceptions are the bonds in quinoxaline and phenazine derivatives, common to the pyrazine and benzene rings, which are fully involved in the benzene ring conjugation and their bond orders do not differ from that in benzene (0.551). The bond orders corresponding to tetrahydropyrazine C–C bonds are approximately equal to C–C bond order in ethane (0.376).

– Terms corresponding to *N*-acetyl bonds are approximately the same as those of all other N–C bonds. The partial conjugation between the nitrogen lone pair and π electrons of the C=O bond is not large.

– Condensed benzene ring significantly lowers the bond order of the neighboring N–C bond. This can be due to the concentration of π electrons in the benzene ring in condensed compounds and their penetration into the N–C bonds.

The common features of the charge distribution obtained from Mulliken population analysis for the molecules studied are depicted in Fig. 4:

– Group charges of $CH_3C=O$ or HC=O moieties are between +0.12 and +0.22 in contrast to +0.36 of hydrogen atom linked to the nitrogen atom in **1**. The group charge of silyl substituents is +0.38.

– All molecules exhibit a large negative charge of about –0.5 on nitrogen.

Isodesmic Energy

The calculated isodesmic energy is negative for all computed reactions. The formation of the dihydropyrazine or tetrahydropyrazine ring has a stabilizing effect (with respect to the components where the conjugation is absent). The antiaromatic compounds can exhibit a negative isodesmic energy[25]. The lower the isodesmic energy, the stronger is the conjugation and aromaticity. The formyl and acetyl substitution on nitrogen atom enlarges the conjugation and the silyl substituents have little effect on the conjugation of the pyrazine ring. Methyl substituents on carbon atoms of

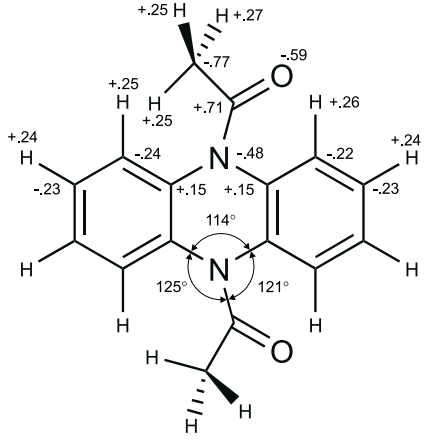


FIG. 4
Charge distribution resulting from the Weinhold's NBO analysis at the B3LYP/6-31G* level and the CNC angles in calculated structure of dihydropyrazine **5**

the pyrazine ring decrease stabilizing conjugation (aromaticity) of the ring due to large structural distortions. Very large effect of the condensed benzene rings, with isodesmic energies close to the nonaromatic systems **9a** and **9b**, suggests that the conjugation be shifted from the pyrazine ring toward the benzene ring(s). In all cases the isodesmic energies show tendency to aromaticity, rather than to expected antiaromaticity of the studied 8 π-electron systems.

Antiaromaticity

The small energy difference[23] between planar and nonplanar structures allows us to classify the 1,4-dihydropyrazines as nonaromatic rather than antiaromatic compounds. The present work supports this classification by the following arguments:

a) Bonds with π electrons have character of isolated double bonds according to their lengths and bond orders.

b) The N–C bonds in the pyrazine ring exhibit only small π-electron densities.

c) Isodesmic energies and structures of 1,4-dihydropyrazines, in comparison to the nonaromatic tetrahydropyrazine systems, exhibit tendency to aromaticity rather than to antiaromaticity.

This result cannot exclude an experimental occurrence of some partial antiaromatic features in these compounds. Some experimental criteria of antiaromaticity[6] follow from a comparison of a wide set of structurally similar compounds. However, only a few 1,4-dihydropyrazines have been yet synthesized despite of the known methods of preparation[6–16,40–46]. Moreover, it is necessary to re-examine the experimental results[9], whether it is not possible to explain them without antiaromaticity arguments, for example by steric interference of some groups in the studied compounds. There is also disagreement between the "computational" criterion[23,24] of antiaromaticity and experimental criteria[6,9] of this property. If a stable conformation of a system is nonplanar, the π-electron conjugation is perturbed and does not exhibit the paratropic effect or low stability due to antiaromaticity.

CONCLUSIONS

The structures, electron distribution, and isodesmic energies do not support antiaromatic character of 1,4-dihydropyrazine derivatives. The structures range from planar to considerably nonplanar boat conformations. The

nonplanarity of diformyl and diacetyl 1,4-dihydropyrazines depends on quality and position of the ring substituents. The anticipated antiaromatic character of 1,4-dihydropyrazine, which results in nonplanar boat or chair conformations, is reversed by the formyl or acetyl *N*-substituents, which put the systems back to planarity if no ring substituent occurs (**2**, **3**). The bond orders of ring C=C bonds exhibit properties of isolated bonds with little deviations due to (anti)aromatic conjugation. This is also supported by small changes of respective bond lengths. The isodesmic energy changes of studied compounds do not show any antiaromatic character of the dihydropyrazine ring. Instead, additional conjugation with acetyl *N*-substituents is observed and the ring *C*-substituents and subsequent structural distortions can lower this conjugation. On the basis of this arguments we propose to classify 1,4-dihydropyrazines as nonaromatic compounds.

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