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Studies on Pyrazinyl-Pyrazylidene Tautomerism of Pyrazine-Acetonitrile Derivatives

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The equilibria between the pyrazinyl and 2(1*H*)-pyrazylidene forms of pyrazineacetonitrile derivatives were studied by IR, ^{1}H-NMR and UV spectroscopy. The excess charges and dipole moments for the two tautomers were calculated by the CNDO/2-MO method.

(Keywords: CNDO/2-MO; IR; PMR; UV)

Untersuchungen über die Pyrazinyl-Pyraziliden-Tautomerie von Pyrazinacetonitril-Derivaten

Die Gleichgewichte zwischen Pyrazinyl- und 2(1*H*)-Pyrazyliden-Formen von Pyrazinacetonitril-Derivaten wurden mittels IR-, PMR- und UV-Spektroskopie untersucht. Die Überschußladungen und Dipolmomente der zwei Tautomeren wurden nach dem CNDO/2-MO-Verfahren berechnet.

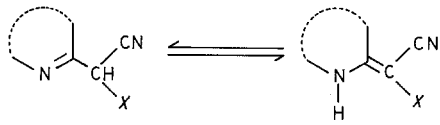
Introduction

Heterocyclic compounds with an active methylene moiety are known to have analgetic and antiinflamatory activity[1,2]. Therefore it seemed of interest to synthetize pyrazine derivatives containing the above mentioned moiety and to study the tautomeric equilibria resulting from the migration of the methine proton to the pyrazine (N_1) nitrogen.

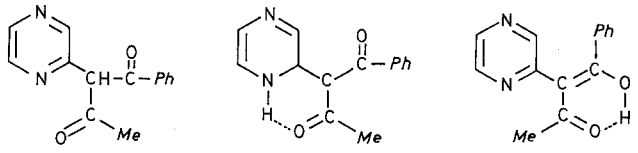
The aromatic nucleophilic substitution of chlorine in 2-chloropyrazine and in 2,6-dichloropyrazine with ethyl cyanoacetate and with malononitrile has been the subject of two recent patents[3,4].

In this paper the tautomeric equilibria between the pyrazinyl and pyrazylidene forms is discussed. It is well known that compounds

containing the CH/CN/X group, when X is COR, COOR, CN, $CONH_2$, exist essentially completely in the N—H tautomeric form.



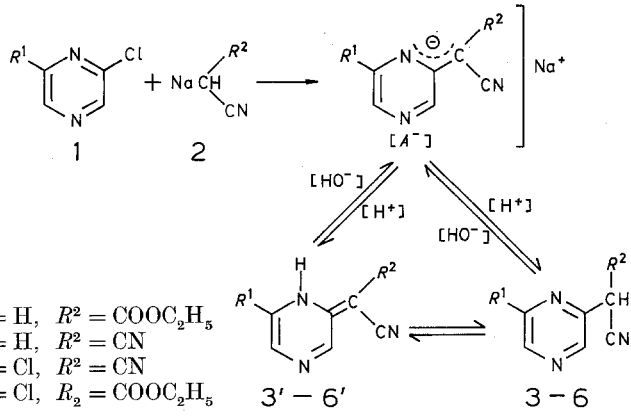
Tautomeric equilibria of this type have been described for the following nitrogen heterocyclic systems: pyridine[5–8], quinoline[9, 10], phenanthroline[10], naphtyridine[1], pyrimidine[11–13], quinoxaline[14, 15]. The spectra of diacylmethylpyrazine[16] show a mixture of three tautomers: CH, NH and OH forms.



Results and Discussion

Spectral Analysis

The UV absorption (Table 1) indicates that the substitution products exist in 2(1 H)-pyrazylidone form **3′**—**5′**. This is due to the protonation of the mesomeric anion (A^-).



3 $R^1 = H$, $R^2 = COOC_2H_5$
4 $R^1 = H$, $R^2 = CN$
5 $R^1 = Cl$, $R^2 = CN$
6 $R^1 = Cl$, $R_2 = COOC_2H_5$

This conclusion has been supported by the observed pH dependence of the UV absorption spectra: In the pH range of 14–10 compound **3** exists completly in an anionic form (A^-). The different UV spectra in the

Table 1. *UV absorption spectra of compounds* **3′**—**5′** *in aqueous solutions*

Compound No. (concentration)	λ_{max}(nm)	ε
3′	227	12 400
	294	22 200
$7.04 \cdot 10^{-5}$ mol dm^{-3}	400	8 500
4′	225	21 100
	293	44 900
$3.7 \cdot 10^{-5}$ mol dm^{-3}	395	14 900
5′	224	13 000
	301	19 800
	390	7 000

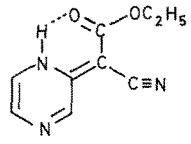
Table 2. *Dependence of the UV absorption characteristics of compound* **3′** *on the pH of the solution*

pH	λ_{max}(nm)	ε
14	240	20 200
	296	22 600
	370	8 400
10	240	20 200
	296	23 000
	370	8 500
8	227	13 600
	294	23 300
	400	9 900
1, 2, 4	225	13 700
	293	23 200
	403	10 000

pH range 1–4 suggests that here protonation of (A^-) takes place (Table 2).

The infrared spectra of compound **3** (Fig. 1), taken in KBr pellets, show a conjugated nitrile band at 2 220 cm^{-1} (=C—C≡N). The ester carbonyl band is absent in the 1 700–1 770 cm^{-1} region which covers normal conjugated and nonconjugated esters. There are strong bands present at 1 645 cm^{-1} (C=O) and 3 040 cm^{-1} (N—H). The characteristic

low frequency of the ester carbonyl suggests that compound **3** exists in the 2(1*H*)-pyrazylidene form **3'**, in which a hydrogen bonding between the N—H moiety and the ester carbonyl is possible. The hydrogen bonding stabilizes the *Z*-configuration.



As the absorption of the N—H group in the ring system was not displayed clearly in the IR spectra (broad band and abnormal absorption at 3040 cm^{-1}) we attempted to detect the N—H group by deuteration.

Upon deuteration the 3040 cm^{-1} band was shifted to 2300 cm^{-1} (N—D) and the strong band at 1610 cm^{-1} moved to 1565 cm^{-1} (N—D). In the ^{1}H-NMR spectra of **3** in $CDCl_3$ and in d_6-*DMSO* the signal due to the **CH**/CN/R^1 group was not detectable.

The IR spectrum of the malononitrile derivative **4** displays a split nitrile absorption at 2190 and 2220 cm^{-1}; this suggests that the two CN groups are spectroscopically different. In the N-deuterated compound **4** instead of the N—H bands at 3220 and 1620 cm^{-1} two bands are visible at 2310 and 1570 cm^{-1}, respectively (Fig. 2).

In the ^{1}H-NMR spectrum of **4** in d_6-*DMSO* the signal of the methine proton was absent.

Reaction of 2,6-dichloropyrazine with malonitrile afforded **5** which existed in the 2(1*H*)-pyrazylidene form **5'** (see UV data).

The UV, IR and ^{1}H-NMR spectra, when considered together, prove the predominance of the 2(1*H*)-pyrazylidene form for the compounds **3'**, **4'** and **5'**.

The reaction of 2,6-dichloropyrazine with ethylcyanoacetate gives the expected ethyl-α-cyano-α-2-(6-chloropyrazinyl)acetate (**6**), but spectroscopic evidence suggests a **6** ⇌ **6'** tautomeric equilibrium. The IR spectrum (neat film) shows a strong band at 1760 cm^{-1} (ester C=O), and a split nitrile absorption at 2210 cm^{-1} (=C—C≡N) and at 2260 cm^{-1} (nonconjugated CH—C≡N).

The relative intensities of the two nitrile bands indicate the tautomer **6** to predominate. In the ^{1}H-NMR spectrum in $CDCl_3$ the —**CH**R^1CN signal at $\delta = 5$ ppm (s, 1H) was detected. If the ^{1}H-NMR spectrum was registered in d_6-*DMSO*, the tautomeric equilibrium shifted and the 2(1*H*)-pyrazylidene form **6'** was favored. Identical UV spectra of **6** in 0.05 *N* HCl and in $CDCl_3$ support this conclusion.

Table 3. *Excess charges and dipole moments calculated by the CNDO/2 method*

Compd.	Atom No.*								Dipole Moment (D)
	1	2	3	4	5	6	7	8	
4	−0.1258	−0.1042	+0.0443	+0.1056	−0.1639	+0.1013	−0.1672	+0.0333	3.56
4′	−0.1420	−0.1010	−0.0475	+0.1530	−0.2634	+0.1617	−0.2669	+0.1452	5.91
5	−0.1097	−0.0992	+0.0476	+0.1100	−0.1625	+0.1052	−0.1665	+0.0374	1.83
5′	−0.1465	−0.1176	−0.0032	+0.1842	−0.2989	+0.1920	−0.3002	+0.1563	4.10
3	−0.1157	−0.0982	−0.0318	+0.1018	−0.1523			+0.0234	3.68
3′	−0.1534	−0.0642	−0.2045	+0.1741	−0.3195			+0.2181	3.57
6	−0.1011	−0.0848	−0.0472	+0.0714	−0.1103			+0.0285	4.75
6′	−0.1589	−0.0834	−0.1670	+0.2109	−0.3614			+0.2274	1.82

* 1: tautomeric N; 2: other N; 3: tautomeric C; 4: C of C≡N; 5: N of C≡N; 6: C of second C≡N in **4**, **4′**, **5**, **5′**; 7: N of second C≡N in **4**, **4′**, **5**, **5′**; 8: tautomeric H (at atom 3 in **3**–**4**, at atom 1 in **3′**–**6′**).

Quantum Chemical Calculations

It seemed worthwhile to compare the spectral data with the electronic structure of the compounds considered. Reliable electronic data may easily be gained from quantum chemical calculations by the CNDO/2-MO method. The program[17, 18] was adapted for the RIAD system computer.

For the pyrazine ring system the bond lengths and angles were assumed according to *Wheatley*[19], whereas the standard values were used for the aut-of-ring moieties. The dipole moments and the excess charges for both types of tautomers **3**, **4**, **5** and **6** are given in Table 3. Based on the data the following regularities were found:

1. In the case of **4** and **5** the excess charge values calculated for the atoms C_3 and H_8 of the C—H acids make the formation of such forms impossible. On the other hand, for **3** and **6** the difference between excess charges on atoms C_3 and H_8 is 0.0552 and 0.0757, respectively. In the last case the existence of the both tautomeric forms at equilibrium is actually observed.

2. Significant differences of excess charges of the N—H moieties for the pyrazylidene tautomers **3'**, **4'**, **5'**, **6'** (0.3715, 0.2872, 0.3028 and 0.3863, resp.) may be meaningful for stabilization.

The correlation between tautomerisation and electronic structure will be further studied with a series of derivatives.

Based on the quantum chemical calculations one may explain why the double absorption band, typical for a nitrile group $=C(CN)_2$, appears for compound **4'**. This is due to the different electron densities at the C and N atoms of the dinitrile system (Table 3).

Comparing the electron densities on the ring nitrogens one can expect the 2(1*H*)-pyrazylidene form to be more easily quarternized. This may be of importance for the analgetic activity of the compounds considered, since it has been suggested[20] that the presence of a nitrogen atom able to quarternize at physiological *pH* is essential for that type of biological action.

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Experimental Part

^{1}-NMR spectra were recorded on a Tesla-Brno BS-487 80 MHz spectrometer with *HMDSO* as internal standard. IR spectra were taken on a Perkin-Elmer M-357 spectrometer in KBr pellets for solids or as a neat film for liquids. UV spectra were recorded on a UV-VIS Carl-Zeiss Jena spectrometer.

Deuterium Exchange

50 mg of **3'** or **4'** were refluxed for 75 h with 10 ml of D_2O. Then the D_2O was evaporated to dryness and the products of deuteration were recrystallized from D_2O. The percentage of deuteration (70%) was determined by NMR.

References

[1] *Pomore N. D.*, J. Med. Chem. **11**, 431 (1968).
[2] *Schwartz N., Mohrbacher R. J.*, USA-Patent 3.901.855 (1975).
[3] *Pilarski B., Foks H.*, Polish-Patent P-232409 (1981).
[4] *Pilarski B., Foks H.*, Polish-Patent P-234716 (1982).
[5] *Junek H.*, Monatsh. Chem. **96**, 2046 (1965).
[6] *Junek H.*, Monatsh. Chem. **95**, 1201 (1964).
[7] *Junek H.*, Monatsh. Chem. **95**, 1473 (1964).
[8] *Gutsche C. D., Voges H. W.*, J. Org. Chem. **32**, 2685 (1967).
[9] *Ishiguro Y., Funakoshi K., Saeki S., Hamana M.*, Heterocycles **14**, 179 (1980).
[10] *Borror A. L., Haeberer A. F.*, J. Org. Chem. **30**, 243 (1965).
[11] *Lapatshev W. W., Zaguliaieva O. A., Mamaiev W. P.*, Khim. Geterotsikl. Soedin. **11**, 1544 (1978).
[12] *Lapatshev W. W., Zaguliaieva O. A., Mamiev W. P.*, Khim. Geterotsikl. Soedin. **3**, 395 (1977).
[13] *Siedova W. F., Mamaiev W. P.*, Khim. Geterotsikl. Soedin. **6**, 827 (1979).
[14] *Hayashi E., Miyagishima T.*, Yakugaku Zasshi **87**, 1103 (1967).
[15] *Mondelli R., Merlini L.*, Tetrahedron **22**, 3253 (1966).
[16] *Chakrabartty S. K., Levine R.*, J. Heterocycl. Chem. **4**, 109 (1967).
[17] *Pople J. A., Segal G. A.*, J. Chem. Phys. **44**, 3289 (1966).
[18] *Dobosh P. A.*, QCPE **11**, 141 (1969).
[19] *Wheatley P.*, Acta Cryst. **10**, 182 (1957).
[20] *Loew G., Burt S., Nomura P., Macleny R.*, ACS Symp. Series No. 112, Computer-Assisted Drug Design (*Olson C., Christoffersen R. E.*, eds.). Amer. Chem. Soc. 1979.