barium hydroxide solution, which was then filtered, and the filtrate diluted with 20 mL of ethanol to give the product as a white precipitate. It was collected by filtration, washed with absolute ethanol, and dried 4 h at 100 °C (0.07 mm): yield 308 mg (15%); UV (0.1 N HCl) 268 nm (log ϵ 8.63), (pH 7) 268 (8.78), (0.1 N NaOH) 268 (7.20); NMR (D_2O) δ 1.3–2.1 (m, $2H_{5'}$ and $2H_{6'}$), 2.3 (m, $2H_{2'}$), 3.96 (m, $H_{4'}$), 6.26 (t, $H_{1'}$), 7.5 (d, J_{HF} = 6 Hz, H_6); LC, C_{18} column (Waters), 0.1 M $NH_4H_2PO_4$ (pH 3.5), retention time 7.8 min. Anal. ($C_{10}H_{11}FN_2O_7P \cdot 1.5Ba \cdot 1.5H_2O$) C, H, N.

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Correlation of Carbonic Anhydrase Inhibitory Activities of Benzenesulfonamides with the Data Obtained by Use of Nitrogen-14 Nuclear Quadrupole Resonance

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Nitrogen-14 nuclear quadrupole resonance (NQR) spectra of several benzenesulfonamides in their solid state are reported and analyzed in the framework of the Townes and Dailey theory. Satisfactory correlations between the ($\sigma_{NH} - \sigma_{NS}$) electron densities at the sulfamyl nitrogen and the in vitro carbonic anhydrase inhibitory activities of the sulfonamides have been found. The correlations are in accord with the results of other studies that show the carbonic anhydrase inhibitory activities to be largely influenced by the electronic property of the sulfamyl group.

It has been well established[1,2] that sulfonamides are active as inhibitors of carbonic anhydrase, the enzyme responsible for the conversion of carbon dioxide and water to hydrogen ion and bicarbonate ion. Since the original observation by Mann and Keilin,[3] other reports[4] have confirmed the fact that high carbonic anhydrase inhibition was obtained in these compounds where the unsubstituted sulfamyl group ($-SO_2NH_2$) was attached directly to an aromatic group (phenyl, naphthyl, or heterocyclic) and that *N*-sulfamyl substitution abolished activity for practical purposes. Kakeya et al.[5] have shown that carbonic anhydrase inhibitory activity of the sulfonamides depends largely on the electronic property of the sulfamyl group. These authors correlate the in vitro inhibitory activity of the sulfonamides with various parameters such as the Hammett σ value, NMR chemical shift of the sulfamyl protons, and pK_a.

In the present work, several benzenesulfonamides have been investigated by nitrogen-14 nuclear quadrupole resonance (NQR) spectroscopy. NQR techniques are well suited to probe the electronic environment of a nucleus and, thus, can be employed to determine the electron distribution at the site of the atom containing the nucleus.[6,7] Correlations of NQR data with the in vitro carbonic anhydrase inhibitory activities of the benzenesulfonamides are considered.

Experimental Section

The NQR signals were detected by using the spin–echo technique.[8,9] Two radio-frequency (rf) pulses of height about 4 kV peak to peak were applied to a coil containing the sample, one pulse (90°) at $t = 0$ and the second pulse (180°) at $t = \tau$, and an echo was observed at $t = 2\tau$. The 90 and 180° pulses were of widths about 20 and 40 μs, respectively, and the interval between the pulses was on the order of 2–3 ms.

The experiments were performed on polycrystalline samples obtained from commercial sources and used as such. All the measurements were made at liquid nitrogen temperature (77 K). Very weak resonances were detected with the aid of a signal averager.[10]

Experimental Results

For nitrogen-14 ($I = 1$), the NQR spectrum consists, in general, of three lines[6,7]

$$\nu_{\pm} = \tfrac{3}{4}e^2qQ(1 \pm \eta/3) \quad (1)$$

and

$$\nu_d = \nu_+ - \nu_- \quad (2)$$

where eQ is the quadrupole moment of the nucleus; e^2qQ and η are, respectively, the quadrupole coupling constant and asymmetry parameter. The quantities q_{xx}, q_{yy}, and $q = q_{zz}$ are the diagonalized components of the electric-field gradient (EFG) tensor at the site of the nitrogen in the principal axis system chosen such that

$$|q_{zz}| \geq |q_{yy}| \geq |q_{xx}|$$

In this notation

$$\eta = (q_{xx} - q_{yy})/q_{zz} \quad (3)$$

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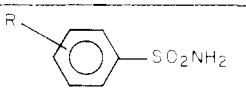
Table I. Nitrogen-14 NQR Spectra of Sulfamyl Nitrogen in Several Sulfonamides at 77 K



compound	R	ν_+, kHz	ν_-, kHz	e^2qQ, dHz	η
sulfanilamide	*p*-NH_2	3478	2538	4011	0.469
		3127[a]	2610[a]	3825[a]	0.270[a]
o-toluenesulfonamide	*o*-CH_3	3690	2704	4263	0.463
metanilamide	*m*-NH_2	3430	2475	3937	0.485
		3340[a]	2560[a]	3933[a]	0.397[a]
benzenesulfonamide	H	3363	2385	3832	0.510
p-toluenesulfonamide	*p*-CH_3	3425	2414	3893	0.519
p-chlorobenzenesulfonamide	*p*-Cl	3453	2434	3925	0.519
p-nitrobenzenesulfonamide	*p*-NO_2	3375	2444	3879	0.480
m-nitrobenzenesulfonamide	*m*-NO_2	3402	2401	3869	0.517
p-methoxybenzenesulfonamide	*p*-OCH_3	3493	2483	3984	0.507
p-carboxybenzenesulfonamide	*p*-COOH	3398	2468	3911	0.476

[a] Values for the nitrogen in the R substituent.

Table I lists the frequencies and related parameters of the compounds investigated in this work.

The presence of nonequivalent nitrogens in some molecules (e.g., sulfanilamide) poses the question of pairing the frequencies. The difference frequency, ν_d, in sulfanilamide was detected (940 kHz). This facilitates the pairing of ν_+ with the appropriate ν_- lines. As can be seen from Table I, the various substituents tend to increase the coupling constant of the sulfamyl nitrogen compared to benzenesulfonamide. Therefore, it is reasonable to assign the larger of the two coupling constants in sulfanilamide to the sulfamyl nitrogen. In the case of the nitrobenzenesulfonamides, only two lines have been detected. These lines have been assigned to the sulfamyl nitrogen because it is known[11] that the coupling constant of the nitrogen of the nitro group is much smaller (on the order of 1 MHz).

Analysis and Discussion

One point of particular difficulty arises in the analysis of NQR data for the amino nitrogen, since the positions of the protons are not well known. The amino group is known to assume different configurations in different compounds. For example, in urea[12] and formamide[13] the amino group is planar, whereas in aniline[14] it is tetragonal. Unfortunately, crystallographic data that would resolve this question are not available for the benzenesulfonamides.

It is possible to calculate the electron distribution in the vicinity of the nitrogen atom in the framework of the theory proposed by Townes and Dailey.[15] However, it is necessary to know the principal axes of the EFG tensor. It is assumed that the sulfamyl nitrogen is in a mixed sp-hybridized state, with ξ as the s character of the lone-pair orbital. Since the lone pair is expected to provide the maximum contribution to the EFG, the z axis of the principal axes is chosen along the direction of the lone pair. The zy plane is so chosen as to bisect the HNH angle. This is clearly arbitrary at this point but will be justified later. It is now possible to write the wave functions and occupation numbers as shown in Table II. The occupation numbers σ_{NS}, σ_{NH}, and l are the electron densities in the N–S and N–H σ bonds and in the lone pair, respectively. The EFG components q_{xx}, q_{yy}, and q_{zz} are calculated using the Townes and Dailey equation[16]

$$q_{zz} = [n_z - \tfrac{1}{2}(n_x + n_y)]q_p \tag{4}$$

and similarly for q_{yy} and q_{xx}, where n_x, n_y, and n_z are the population of the nitrogen p_x, p_y, and p_z orbitals; q_p is the magnitude of the maximum component of the EFG for a single 2p electron. The quantities n_x, n_y, and n_z are related to the occupation numbers given in Table II as follows:

Table II. Occupation Numbers and Mixed s-p Hybrid Wave Functions for the Amino Group in SO_2NH_2

wave functions	occupation no.
$\psi_l = \xi^{1/2}s + (1-\xi)^{1/2}p_z$	l
$\psi_{NS} = \tfrac{1}{3}(1-\xi)^{1/2}s - \tfrac{1}{3}\xi^{1/2}p_z - \tfrac{2}{3}^{1/2}p_y$	σ_{NS}
$\psi_{NH_1} =$ $\tfrac{1}{3}(1-\xi)^{1/2}s - \tfrac{1}{3}\xi^{1/2}p_z + \tfrac{1}{6}^{1/2}p_y - \tfrac{1}{2}^{1/2}p_x$	σ_{NH}
$\psi_{NH_2} =$ $\tfrac{1}{3}(1-\xi)^{1/2}s - \tfrac{1}{3}\xi^{1/2}p_z + \tfrac{1}{6}^{1/2}p_y + \tfrac{1}{2}^{1/2}p_x$	σ_{NH}

$$n_x = \sigma_{NH}$$

$$n_y = \tfrac{1}{3}\sigma_{NH} + \tfrac{2}{3}\sigma_{NS} \tag{5}$$

and

$$n_z = \xi(\tfrac{2}{3}\sigma_{NH} + \tfrac{1}{3}\sigma_{NS}) + (1-\xi)l$$

Using eq 4 and 5, one obtains

$$(e^2qQ/e^2q_pQ) = (l - \bar{\sigma})(1 - \xi) \tag{6}$$

and

$$(e^2qQ/e^2q_pQ)\eta = (\sigma_{NH} - \sigma_{NS}) \tag{7}$$

where $\bar{\sigma} = \tfrac{1}{3}\sigma_{NS} + \tfrac{2}{3}\sigma_{NH}$ is the average of all three σ electron densities. From eq 1, 2, and 7 one obtains

$$\sigma_{NH} - \sigma_{NS} = 2\nu_d/e^2q_pQ \tag{8}$$

If the axes x and y of the principal axes are interchanged, eq 8 would become

$$\sigma_{NS} - \sigma_{NH} = 2\nu_d/e^2q_pQ \tag{9}$$

Since sulfur is more electronegative than hydrogen, it is expected that $\sigma_{NH} > \sigma_{NS}$. Therefore, eq 8 should be applicable rather than eq 9.

It can be seen from eq 6 that $(l - \bar{\sigma})$ depends upon the hybridization parameter ξ which varies from 0 to 0.25 as the hybridization of the sulfamyl nitrogen varies from sp^2 to sp^3. However, $\sigma_{NH} - \sigma_{NS}$ is independent of ξ (see eq 8).

The quantity e^2q_pQ for nitrogen is not known accurately. Different authors have used different values ranging from 8 to 12 MHz.[6,7] In the present work a value of 8.4 MHz has been assumed for e^2q_pQ.[7,16] This is a serious approximation if one is interested in absolute charge densities but is of negligible importance when comparisons are made

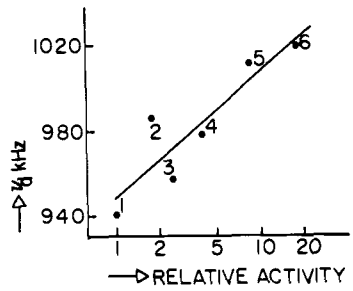


Figure 1. Plot of ν_d which is $\sigma_{NH} - \sigma_{NS}$ against relative carbonic anhydrase inhibitory activities of benzenesulfonamides compared to sulfanilamide.[17]

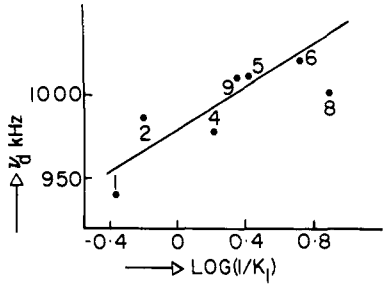


Figure 2. Plot of ν_d against $\log(1/K_1)$ at 0.2 °C, where K_1 is the carbonic anhydrase inhibition constant ($\times 10^{-5}$ M) and $1/K_1$ is proportional to the inhibitory activity.[5]

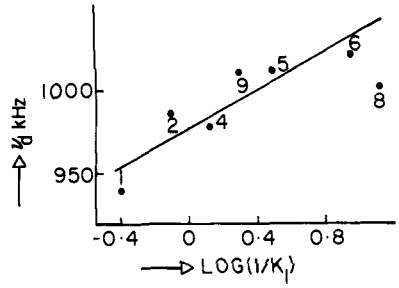


Figure 3. Plot of ν_d against $\log(1/K_1)$ at 15 °C.[5]

of similarly structured molecules using the same value of e^2q_pQ.

Table III lists the NQR difference frequency, ν_d, which is a measure of $\sigma_{NH} - \sigma_{NS}$ (see eq 8) and the in vitro carbonic anhydrase inhibitory activities of several benzenesulfonamides. Values in column a of Table III are the data from Miller et al.,[17] reported in terms of their relative activity compared with sulfanilamide, for 50% inhibition. Columns b and c are the data from Kakeya et al.,[5] given as $\log(1/K_1)$ at 0.2 and 15 °C, respectively, where K_1 is the carbonic anhydrase inhibition constant ($\times 10^{-5}$ M) and $1/K_1$ is proportional to the in vitro carbonic anhydrase inhibitory activity.

Figures 1–3 are the plots of ν_d against the in vitro carbonic anhydrase inhibitory activities data in columns a–c, respectively, of Table III. The numbers on the plot correspond to the numbers of the compounds in Table III. The regression equations (excluding point 8) obtained by the method of least squares are as follows. Figure 1: ν_d (kHz) = 59.8 log(activity) + 947, (n = 6), with a correlation coefficient r = 0.89 and the standard deviation from the line s = 16 kHz; Figure 2: ν_d (kHz) = 63.7 $\log(1/K_1)$ + 979, (n = 6), with r = 0.86 and s = 17 kHz; and Figure 3: ν_d (kHz) = 56 $\log(1/K_1)$ + 978, (n = 6), with r = 0.88 and s = 16 kHz, where n = 6 is the number of points used in the regression analysis. Points 7 (not shown on the plot) and 8 show considerable deviation from the expected trend, with point 7 showing a much larger deviation than point 8. The fact that these two points correspond to the two nitro compounds suggests that the deviations might be due to the presence of intermolecular hydrogen bonds in these compounds in their solid state. Although no crystallographic data are available for these compounds, it is known that hydrogen bonds of the type N–H···O exist in the nitroanilines,[18,19] $O_2NC_6H_4NH_2$. Assuming similar hydrogen bonding in the nitrobenzenesulfonamides, $O_2NC_6H_4SO_2NH_2$, it can be seen that such hydrogen bonds, where N is the proton donor and O is the proton acceptor, would lead to an increase in the value of σ_{NH} because of the contribution of the charge-transfer structure N^-–H···O^+. Some theoretical CNDO/2 calculations[20,21] on the electronic structure of hydrogen bonds of the type N–H···O reveal that nitrogen gains σ electrons with an associated loss of π electrons. An increase in σ_{NH} should lead to an increase in the value of ν_d (see eq 8). This implies that in the absence of hydrogen bonding the value of ν_d would be still smaller, leading to a larger deviation. Therefore, it is clear that the scattering of the points corresponding to the nitrobenzenesulfonamides cannot be explained by invoking the presence of hydrogen bonds in these compounds.

Table III. NQR Difference Frequency ν_d and Carbonic Anhydrase Inhibitory Activities of Benzenesulfonamides

compound	ν_d, kHz	carbonic anhydrase inhib act.[a] a	b	c
sulfanilamide (1)	940	1	−0.363	−0.398
o-toluenesulfonamide (2)	986	1.8	−0.204	−0.080
metanilamide (3)	955	2.5		
benzenesulfonamide (4)	978	4.0	0.215	0.124
p-toluenesulfonamide (5)	1011	8.5	0.420	0.496
p-chlorobenzenesulfonamide (6)	1019	18	0.721	0.959
p-nitrobenzenesulfonamide (7)	931	23	1.046	1.260
m-nitrobenzenesulfonamide (8)	1001		0.886	1.125
p-methoxybenzenesulfonamide (9)	1010		0.347	0.301

[a] Column a: Relative carbonic anhydrase inhibitory activity compared with sulfanilamide for 50% inhibition. Data from ref 17. Columns b and c: Data from ref 5 given as $\log(1/K_1)$ at 0.2 and at 15 °C, respectively, where K_1 is the carbonic anhydrase inhibition constant ($\times 10^{-5}$ M) and $1/K_1$ is proportional to the inhibitory activity.

In their structure–activity correlation studies of benzenesulfonamides, Kakeya et al.[5] attribute the deviation of *p*-nitrobenzenesulfonamide as being due to the increased resonance interaction between the nitro group and the sulfamyl group. The nitro group, being an electron-attracting group, withdraws electrons from the sulfamyl group, leading to a reduced π electron density at the sulfamyl nitrogen. Thus, the sulfamyl nitrogen would become more σ electronegative, with the result that the σ electron density at the nitrogen increases. The low value of ν_d in *p*-nitrobenzenesulfonamide suggests that the increase of σ_{NS} is larger than that of σ_{NH}. Although a substituent in the meta position is structurally unable to enter into resonance conjugation with the sulfamyl group, it is known that the resonance effect of the meta group is not zero.[22] The much smaller scattering of the *m*-nitrobenzenesulfonamide compared to *p*-nitrobenzenesulfonamide apparently reflects this trend. An alternative explanation for the deviation could be that the mode of

action of the nitro compounds is different from that of the other compounds. The present NQR studies do not yield information on which a unique explanation for the deviation can be based.

From Figures 1-3 it can be seen that there is a significant correlation between ν_d, which is a measure of the ($\sigma_{NH} - \sigma_{NS}$) electron density at the sulfamyl nitrogen (see eq 8), and the in vitro carbonic anhydrase inhibitory activity of the benzenesulfonamides, with the exception of the nitro compounds. It appears that an increase of σ_{NH} or a decrease of σ_{NS} (or both) results in increased activity.

It has been postulated[23] that the carbonic anhydrase inhibitors attach themselves to the active site of the enzyme through hydrogen bonds formed by the N-H bonds of the sulfamyl group. A hydrogen bond of the type N-H···X, where X is a proton acceptor, results in an increase in the value of σ_{NH}. Thus, σ_{NH} can be taken to be a measure of the strength of the hydrogen bond formed by the N-H bond. The correlation between ν_d, which is a measure of $\sigma_{NH} - \sigma_{NS}$ electron density, and the carbonic anhydrase inhibitory activities of the benzenesulfonamides suggests the possibility that the activities of the sulfonamides parallel the strength of the hydrogen bonds formed between the N-H bonds of the sulfamyl group and the active site of the enzyme.

Conclusion

Nitrogen-14 NQR studies of several benzenesulfonamides in their solid state reveal significant correlations between the $\sigma_{NH} - \sigma_{NS}$ electron density at the sulfamyl nitrogen and the in vitro carbonic anhydrase inhibitory activities of the sulfonamides. It appears that the activities of the sulfonamides depend largely upon the electronic property of the sulfamyl group. The nitro compounds show considerable deviation from the expected trend. This cannot be explained by invoking the presence of hydrogen bonds in these compounds. The deviations are probably due to increased resonance conjugation between the nitro group and the sulfamyl group or to a different mode of action.

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11-Oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic Acid, an Orally Active Antiallergy Agent

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A new series of 11-oxo-11*H*-pyrido[2,1-*b*]quinazolinecarboxylic acids and related analogues has been synthesized and evaluated as potential antiallergy agents. In the rat PCA test, 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acid is orally active and more potent than cromolyn sodium or doxantrazole intravenously.

Some 11-oxo-11*H*-pyrido[2,1-*b*]quinazolinecarboxylic acids have been synthesized and evaluated as potential antiallergy agents. Their activities were compared with two clinically active agents, cromolyn sodium and doxantrazole. While cromolyn sodium is ineffective orally, it is useful when insufflated as a powder. Doxantrazole was reported to be orally active in early single-dose clinical trials.[1,2]

The reversible narrowing of bronchial airways and accompanying edema in bronchial mucosa observed in

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