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Determination of the Volume Susceptibility of the Characterisitic Excretion in Stomach Cancer Urine by Chemical Shifts[1]

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Abstract

Recently NMR analyses of human urine show that the four proton NMR signals between 7 ppm and 8 ppm more frequently appear in stomach cancer urine than in normal and other diseased urine. These four NMR signals are found to be given by 7.25, 7.38, 7.63 and 7.80 in ppm. The calculations of spin coupling constants show that the NMR signals are identified as the four aromatic proton NMR signals of m-hydroxyphenyl rather than the ones of p-hydroxyphenyl. With this frequent appearance in the cancer urine, the cancer diagnosis has been made. In the present work, an attempt is made to determine the total volume susceptibility of the four aromatic proton NMR signals of the excreted m-hydroxyphenyl. The results of the attempt show that the volume susceptibilities of the above given values are as follows : 10.01×10^{-6}, 10.07×10^{-6}, 10.19×10^{-6} and 10.27×10^{-6}. Hence its total susceptibility is 10.27×10^{-6}.

Introduction

According to the recent NMR analysis[1,2)] of human urine, it is observed that the four proton NMR signals between 7 ppm and 8 ppm which are relatively broader and higher more frequently appear in stomach cancer urine than in normal and other diseased urine. By using the frequent appearance and the higher concentration of the excretion corresponding to the signals regarded as a cancer marker, a cancer diagnosis has been made[2].

The above four proton NMR signals[2)] are found to be given by 7.25, 7.38, 7.63, and 7.80 in ppm. The following figure shows the NMR signal distribution of the stomach cancer urine :

In order to identify the excretion, the NMR experiments have been done to obtain the four aromatic proton NMR signals of m-hydroxyphenyl of DL-m-tyrosine and p-hydroxyphenyl of L-tyrosine. They are as follows :

1. This work is supported by Hanyang University research foundation granted in 1997.
2. Refer the US paptent documents(No. 5,066,601 and No.5,094,836) and the Japanese patent documents (No. 1,942,648 and No. 1,976,252).

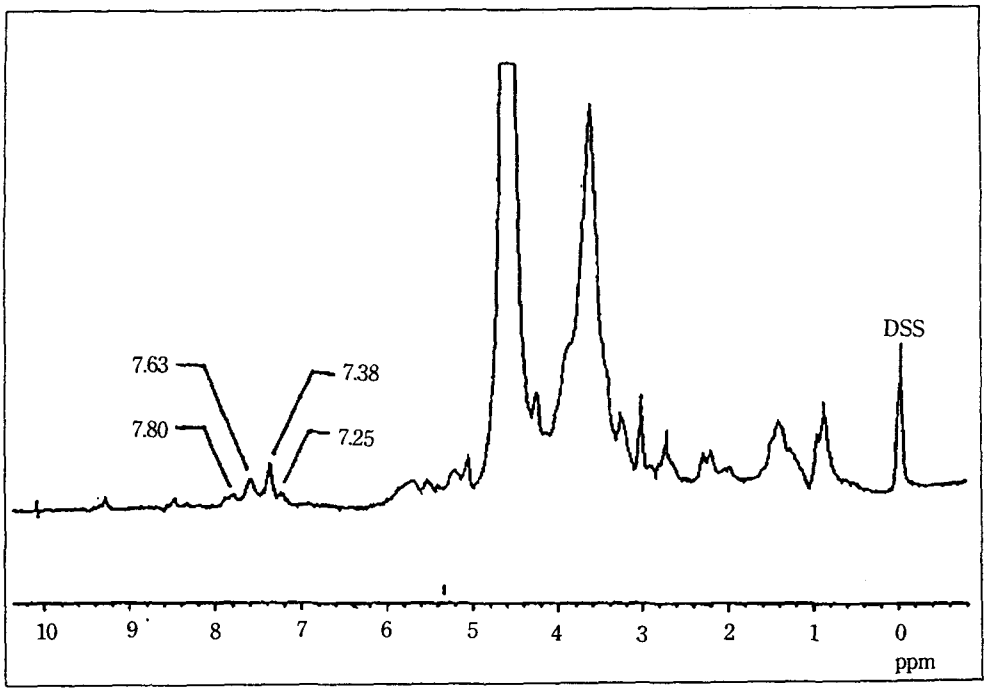

Fig. 1. Proton NMR signal distribution of a patient's urine of stomach cancer with bilirubinuria

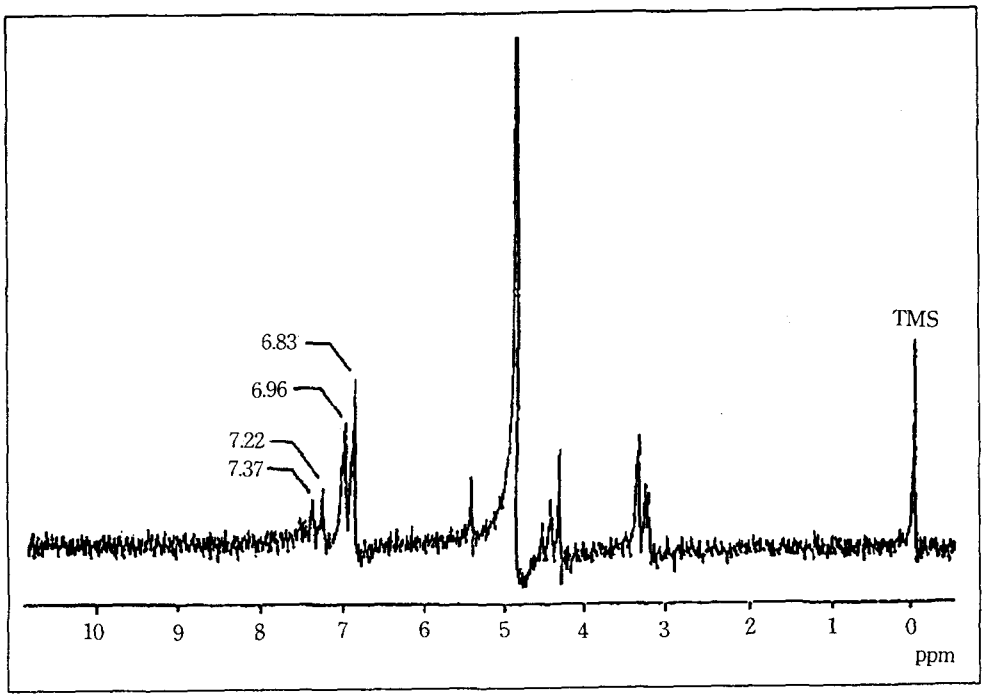

Fig. 2. Proton NMR signal distribution of DL-m-tyrosine

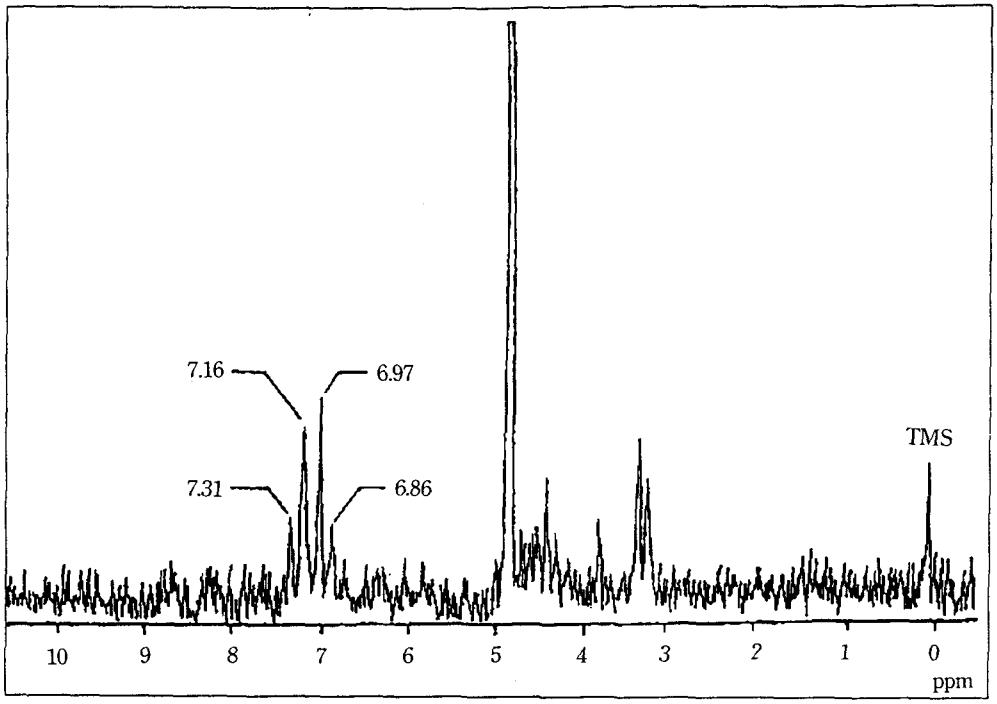

Fig. 3. Proton NMR signal distribution of L-tyrosine

The respective signal values of the three figures are listed in the following table for comparison :

Table 1. The proton NMR signals of the excretion of urine and the hydroxyphenyl samples.

Excretion and hydroxyphenyl	Proton NMR signal (ppm)			
Stomach cancer urine	7.80	7.63	7.38	7.25
m-hydroxyphenyl	7.37	7.22	6.96	6.83
p-hydroxyphenyl	7.31	7.16	6.97	6.86

From Table 1 one can notice that none of the NMR signals of both m- and p-hydroxyphenyl coincide with the ones of the excretion. However according to the results of the color reactions of the substances together with the stomach cancer urine caused by the reagents developed for cancer diagnosis introduced in the patent documents indicated in the footnote, they equally show the characterisitic coloration which is red. Since the spin coupling constants of the NMR signals of given paramagnetic substances are characteristic, they can be used for identification, it is attempted to obtain the spin coupling constants of the foregoing three substances.

The constants are listed in the following table :

Table 2. The spin coupling constants at the four proton NMR signals of the excretion and the two substances

Excretion in cancer urine and hydroxyphenyl	Spin coupling constants (ppm)		
Excretion	0.17	0.25	0.13
m-hydroxyphenyl	0.15	0.26	0.13
p-hydroxyphenyl	0.15	0.19	0.11

Here it must be noted that each spin coupling constant is expressed in ppm simply for comparison rather than in frequency used customarily.

As shown in Table 2, the first two rows are so close to each other. From this, although it has been known that the excretions of tyrosine species in human urine are tyrosine and its metabolites such as p-hydroxyphenyl-pyruvate, -lactate, -acetate, and other tyrosine derivatives[4], it has come to the conclusion that the substance corresponding to the four proton NMR signals of the stomach cancer urine is the one of m-hydroxyphenyl rather than p-hydroxyphenyl which has commonly been known to be one of the tyrosine metabolites in human urine.

In this work, an attempt is made to the total volume susceptibility of the identified excretion with which one might find a new way of diagnosing cancer. The result of the attempt shows that the total volume susceptibility is found to be given by 40.54×10^{-6}.

Method (Determination of Volume Susceptibility)

The magnetic shielding constants[3] is given by

$$\sigma=\sigma_{ref}+\delta \tag{1}$$

where srefis the magnetic shielding constant of the sample used as a reference standard for chemical shift measurement and d is the chemical shift.

$$\sigma=\frac{2\pi}{3}K=\sigma_{ref}+\delta \tag{2}$$

where K is the volume susceptibility of a sample.

In order to practically to use Eq.(2), the value of sref in Eq.(2) must, first of all, be determined. From Eq.(2), s_{ref} is given by

$$\sigma_{ref}\cong2.09K-\delta \tag{3}$$

As shown in Fig.4, the chemical shift δ of water is δ=4.72 ppm and the magnitude(5) of the volume susceptibility of water, K, is given by $K=8.8\times10^{-6}$.

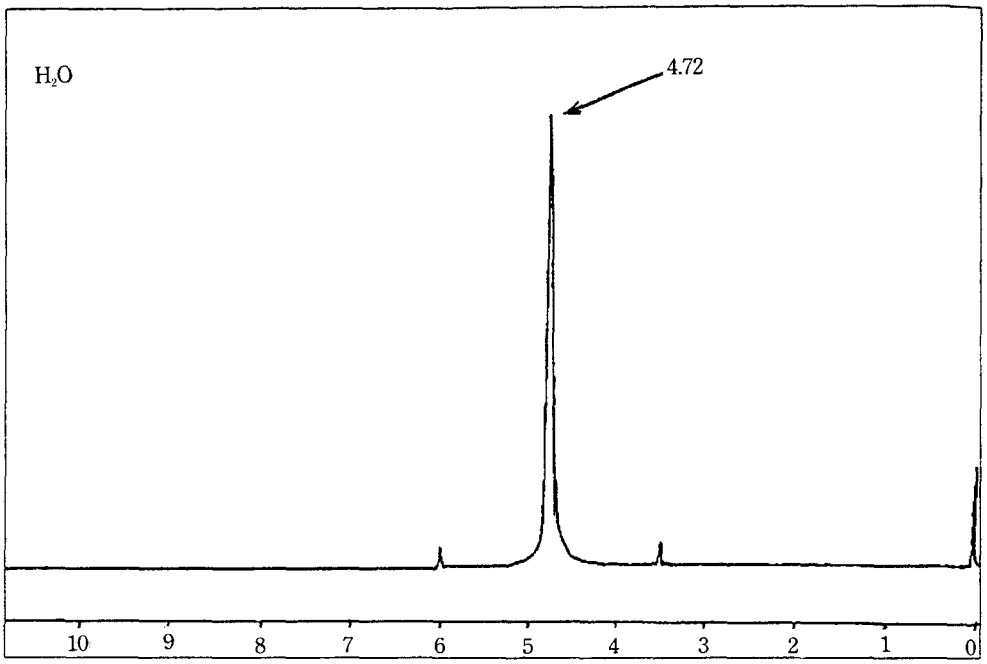

Fig. 4. Observed proton NMR signal distribution of H_2O in ppm measured at room temperature

Substituting these values into Eq.(3), sref in ppm is found to be given by

$$\sigma_{ref} = 13.67 \times 10^{-6}$$

Here the value of sref is the one of DSS taken as an internal reference standard for chemical measurement. Hence Eq.(2) can be written as

$$2.09K = 13.67 \times 10^{-6} + \delta \tag{4}$$

from which K is given by

$$K = \frac{13.67 \times 10^{-6} + \delta}{2.09} \tag{5}$$

When each of the δ's shown in Fig.1 to 3 are substituted into Eq.(5), the corresponding K's can be determined.

Since the main purpose of the present work is to find the total volume susceptibility of the excretion of the stomach cancer urine shown in Fig.1, the respective susceptibilities of the four aromatic proton NMR signals of the excretion are listed in the following table :

Hence the total volume susceptibility K_{total} of the excretion is given by

$$K_{total} = 40.54 \times 10^{-6}$$

Results and Discussion

It must further be examined whether all the procedures taken for obtaining the total volume susceptibility of the excretion are correct. As indicated in the introduction, the reagents developed for cancer diagnosis have a good sensitivity and specificity; both its sensitivity and specificity are above 75% on an average. For this the excretion of the stomach cancer urine is truly regarded as a cancer marker. Being based on this fact, the present work may lead to some other possible ways of diagnosing cancer by use of the value of the volume susceptibility of the excretion rather than by use of the reagents.

References

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화학적 이동에 의한 위암뇨의 특성배설물의 체적자화율 결정

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초 록

위암뇨에서 7 ppm과 8 ppm사이에 네 개의 특성 핵자기공명신호가 나타남을 최근의 핵자기공명분석으로 알게 되었고, 이 신호들은 정상뇨와 타질병 환자뇨에 비하여 자주 일어남을 발견하였다. 이 네 개의 신호들은 각각 7.25 ppm, 7.38 ppm, 7.63 ppm 그리고 7.80 ppm이었다. 스핀결합상수의 계산에 의하면, 이 네 개의 공명신호는 종래에 알려졌던 p-hydroxyphenyl이 아니라 m-hydroxyphenyl임이 밝혀졌다. 본 연구에서는 핵자기공명신호가 자주 일어남을 이용하여 암진단을 가능케 하였고, 이들 네 방향족 핵자기공명신호의 체적자화율을 측정하여 타 목적에 기여할 수 있게 하였다. 체적자화율의 측정 결과는 각각 10.01×10^{-6}, 10.07×10^{-6}, 10.19×10^{-6} 그리고 10.27×10^{-6}이었고, m-hydroxyphenyl의 총체적자화율은 10.27×10^{-6}이었다.