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^{1}H-NUCLEAR MAGNETIC RESONANCE (NMR) STUDY OF PIROXICAM-CYCLODEXTRINS INCLUSION COMPLEXES

N.M.Omar, A.N. Ahmed, H.Ueda[*]*, and S.M.El-Gizawy*
Faculty of Pharmacy, Department of Pharmaceutical Chemistry.
Assiut University, Assiut, Egypt.
[*]*Hoshi Institute of Pharmaceutical Sciences, Tokyo, Japan.*

ABSTRACT

A Structural study of the inclusion compounds of piroxicam with cyclodextrins (α-, β-and γ-) in different molar ratios was studied by means of ^{1}H-nuclear magnetic resonance (NMR) spectroscopy. The change in the chemical shift suggested that the drug pyridine moiety was included in the cavity of cyclodextrins and most of the protons shifted to lower field with increasing the concentration of cyclodextrins. Plots of the molar ratio of cyclodextrins vs. the change in the chemical shift of piroxicam indicated that a 1:1 complex was formed.

INTRODUCTION

Cyclodextrins have received considerable attention because they can modify the physical and chemical properties of drug molecules through inclusion complexation[1,2]. Extensive studies on inclusion compounds of various medicinally useful molecules with cyclodextrins have been reported[3-10]. It has been shown that the force holding together these complexes seems to be van der Waal's, hydrogen bonding as well as hydrophobic interactions and that the magnitude of these forces

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depends upon the geometry of the host and guest molecules[11].

A structural study of the inclusion compounds of various drugs with cyclodextrins in aqueous solution and in solid state was confirmed by means of proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy[12-17].

In the present work, the ^{1}H-NMR technique was used to probe the structure of inclusion compounds of piroxicam with cyclodextrins (α -, B-and γ-).

EXPERIMENTAL

Materials :

The following materials were used; 99.8% deuterium oxide (Merck), sodium hydroxide-d_1 solution (about 40% sodium deutorium oxide in D_2O, Merck). Highly purified piroxicam (Pfizer Inc., Japan) and α -, B- and γ -cyclodextrins were obtained as gifts from Nihon Shokuhin Kako, Co., Ltd., Tokyo, Japan.

The inclusion compounds (piroxicam- α-CyD, piroxicam-B-CYD and piroxicam-γ CyD) were prepared by coprecipitation method[16], 3.3×10^{-3}M of piroxicam and 1×10^{-3}M of CyDs in water was agitated well for 24 hr. at room temperature. The inclusion compounds (precipitated as a microcrystalline powder) were filtered off, washed with little water, and then dried under vacuum at room temperature for 24 hr.

Methods :

The ^{1}H spectra were observed with a JNM-Fx 100 spectrometer operating at ^{1}H-99.65 MHz in the pulsed Fourier transform mode. All spectra were obtained at 25 ± 0.5°C. The ^{1}H-chemical shifts are given relative to external tetramethylsilane within ± 0.002 ppm.

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RESULTS AND DISCUSSION

It is well known that the molecule of cyclodextrin (CyD) has a torus shape with a central void of a few angstroms diameter[18]. The internal surface is relatively hydrophobic, and cyclodextrin can accomodate various molecules as guests in the nonpolar cavity by noncovalent interactions[18]. If an aromatic group complexes with cyclodextrins, it is expected that some of cyclodextrin protons will experience a chemical shift that depends on the average location of the probe with respect to the cyclodextrin structure. The present work aimed to study the inclusion compound of piroxicam with cyclodextrins (α -, B-and γ -) in different molar ratios by means of ^{1}H-NMR spectroscopy. The ^{1}H-NMR analysis of aqueous solutions of piroxicam with α-CyD, B-CyD, and γ-CyD reveals substantial differences of the ^{1}H-resonance in both the probe and the CyD.

Within the spectral region of 3.8-4.08 pmm (δ ,100 MHz) Figure (1a-c) the H-5 signal of CyD (α -, B-and γ -) could not be directly observed since it overlapped with other H-3 and H-6 of cyclodextrins signals when low molar concentrations of the host molecules were investigated. However, when 1:1 molar ratios of the host: guest molecule were used, a sharp signal assigned to H-5 in α-CyD and B-CyD was monitored shifted upfield on increasing the molar concentration of piroxicam more than 1:1 molar ratios. Simultaneously, the H-1 and H-3 signal behaved similarly, Figures(1a-c).

Figures(2a-c) show the effect of cyclodextrins (α-, B-and γ -) in different molar ratios on the ^{1}H-NMR spectrum of piroxicam in 0.2 N NaOD. All the protons of piroxicam pyridine moiety (H-a, H-b, H-c and H-d) shifted to lower field on increasing the concentration of CyDs. Similar chemical shift changes have been observed for the benzenoid protons of piroxicam (H-1, H-2, H-3 and H-4). However, that

effect was more pronounced in the case of H-4 and this may be attributed to the diamagnetic anisotropy of the phenyl moiety. It is evidently clear that there was an overlap between the H-1, H-2 and H-3 of the benzenoid protons with H-C of pyridine portion of piroxicam. In the case of piroxicam-α-CyD complex, the H-a proton shows substantial major shift ($\sim$ 0.16), like the H-d proton ($\sim$ 0.13), while the H-b proton and H-C proton of the pyridine moiety of piroxicam show a somewhat smaller down-field shift ($\sim$ 0.07-0.1). The H-4 of the benzenoid protons shows the most substantial downfield chemical shift ($\sim$ 0.12) while H-1, H-2 and H-3 benzenoid protons did not show any significant shift , Figures (2a-C). On the other hand, for the piroxicam-B-CyD and piroxicam - γ-CyD complexes, the H-a proton shows downfield shifts ($\sim$ 0.09-0.12), while the H-b, H-c and H-d protons show a somewhat smaller downfield shift as compa-ring to piroxicam-α CyD complex ($\sim$ 0.08-0.06). The H-4 proton keeps the same downfield shift as in case of α-CyD ($\sim$ 0.12).

From plotting the molar ratios of the cyclodextrins investigated versus the corresponding chemical shift values of the different protons, it is plausible to assume that the presented complexation is based on 1:1 molar ratio and that inclusion of the piroxicam molecule is mostly dependant on the pyridine moiety rather than the benzenoid skeleton.

^{1}H-Nuclear Magnetic Resonance (NMR) Study of Piroxicam-Cyclodextrins Inclusion Complexes.

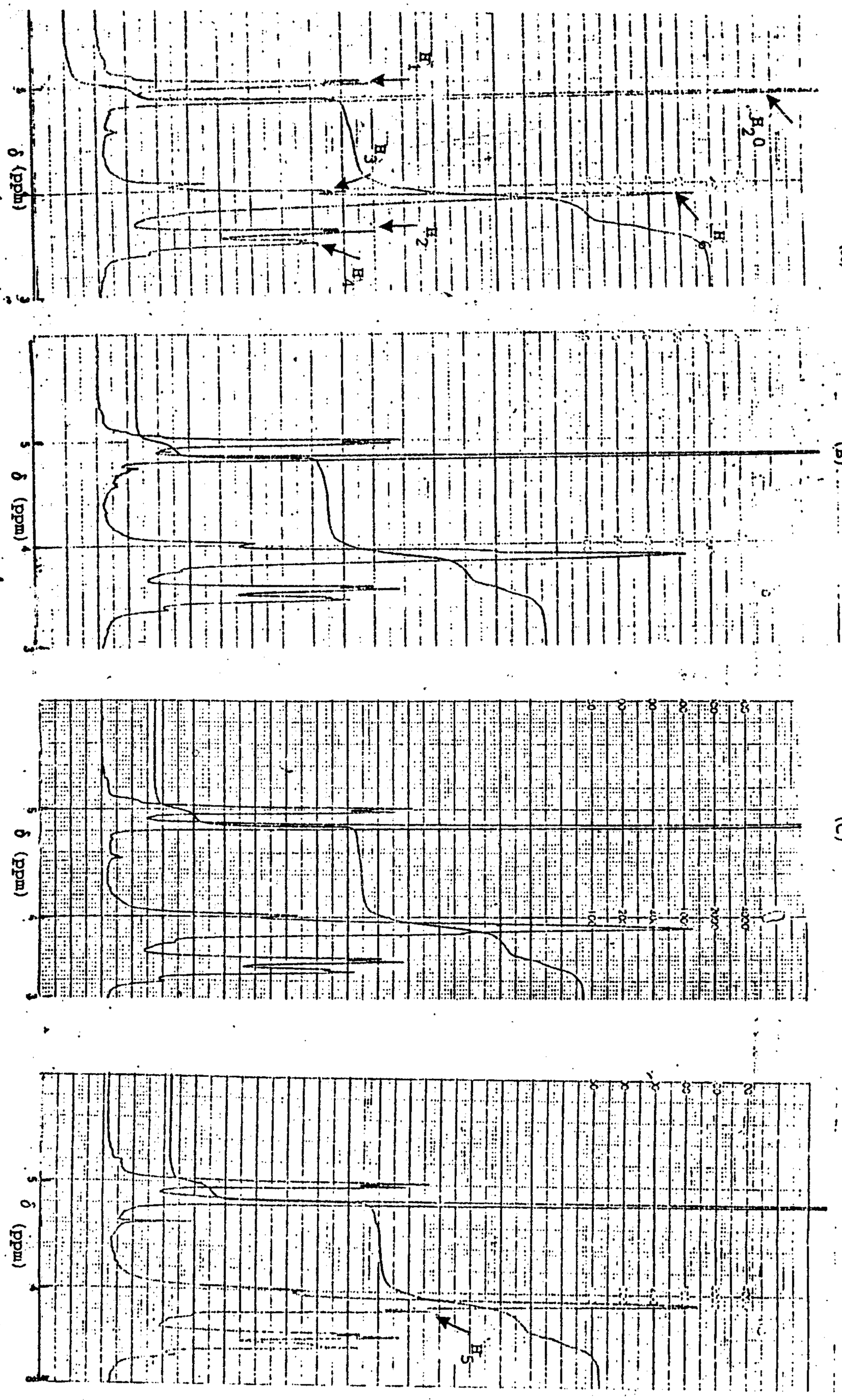

Fig. 1 a : ^{1}H-NMR Spectra of α-Cyclodextrin (1×10^{-1} M) Containing Various Amounts of Piroxicam. Molar ratio of piroxicam-cyclodextrin: (A) 0.00, (B) 0.50, (C) 0.75, (D) 1.00 Solvent 0.2 N NaOD in D_2O.

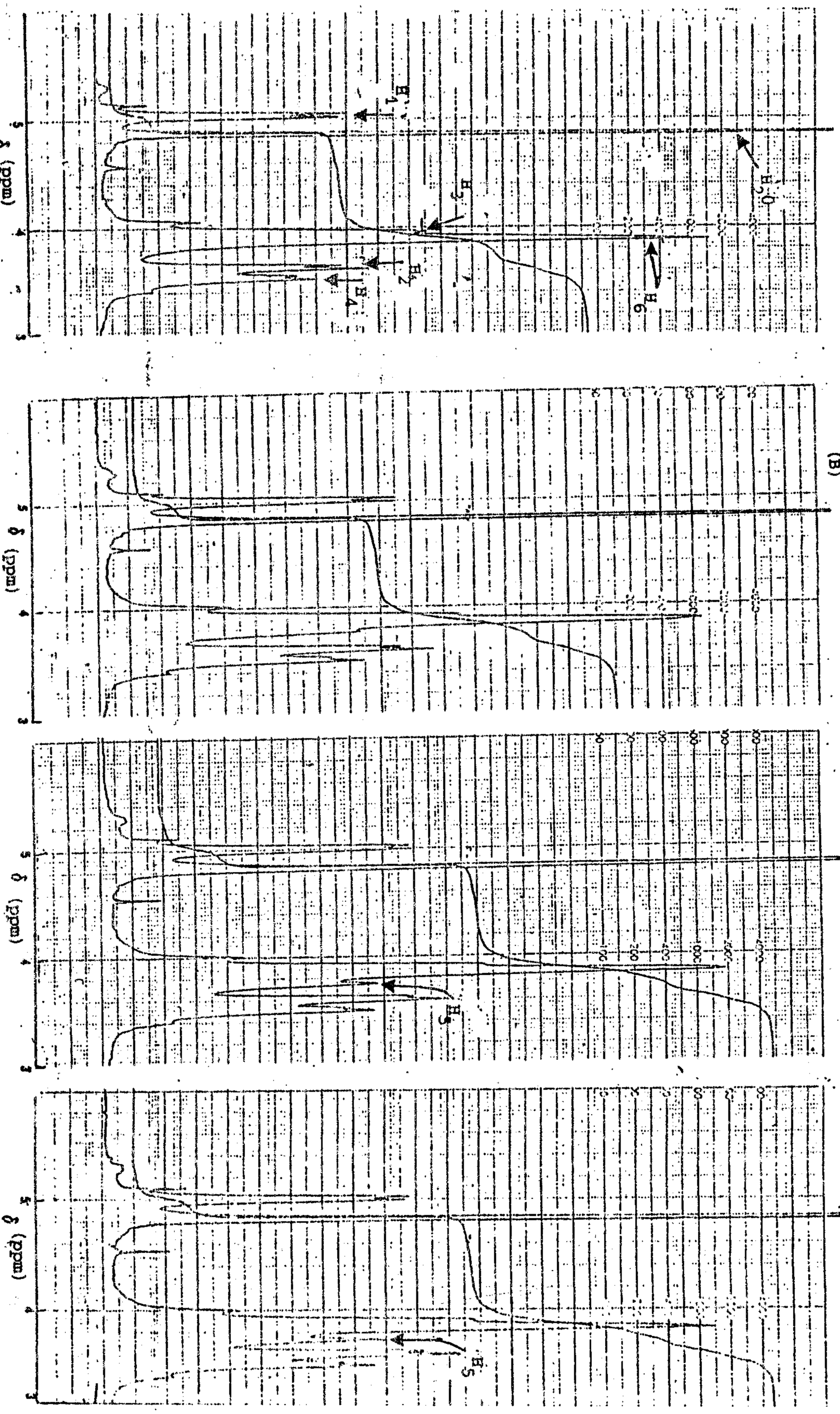

Fig. 1b: ^{1}H-NMR Spectra of β- Cyclodextrin($1x10^{-1}$ M) Containing Various Amounts of Piroxicam-cyclodextrin: (A) 0.00, (B) 0.50, (C) 0.75, (D) 1.00 Molar ratio of piroxicam-cyclodextrin: Solvent 0.2 N NaOD in D_2O.

^{1}H-Nuclear Magnetic Resonance (NMR) Study of Piroxicam-Cyclodextrins Inclusion Complexes.

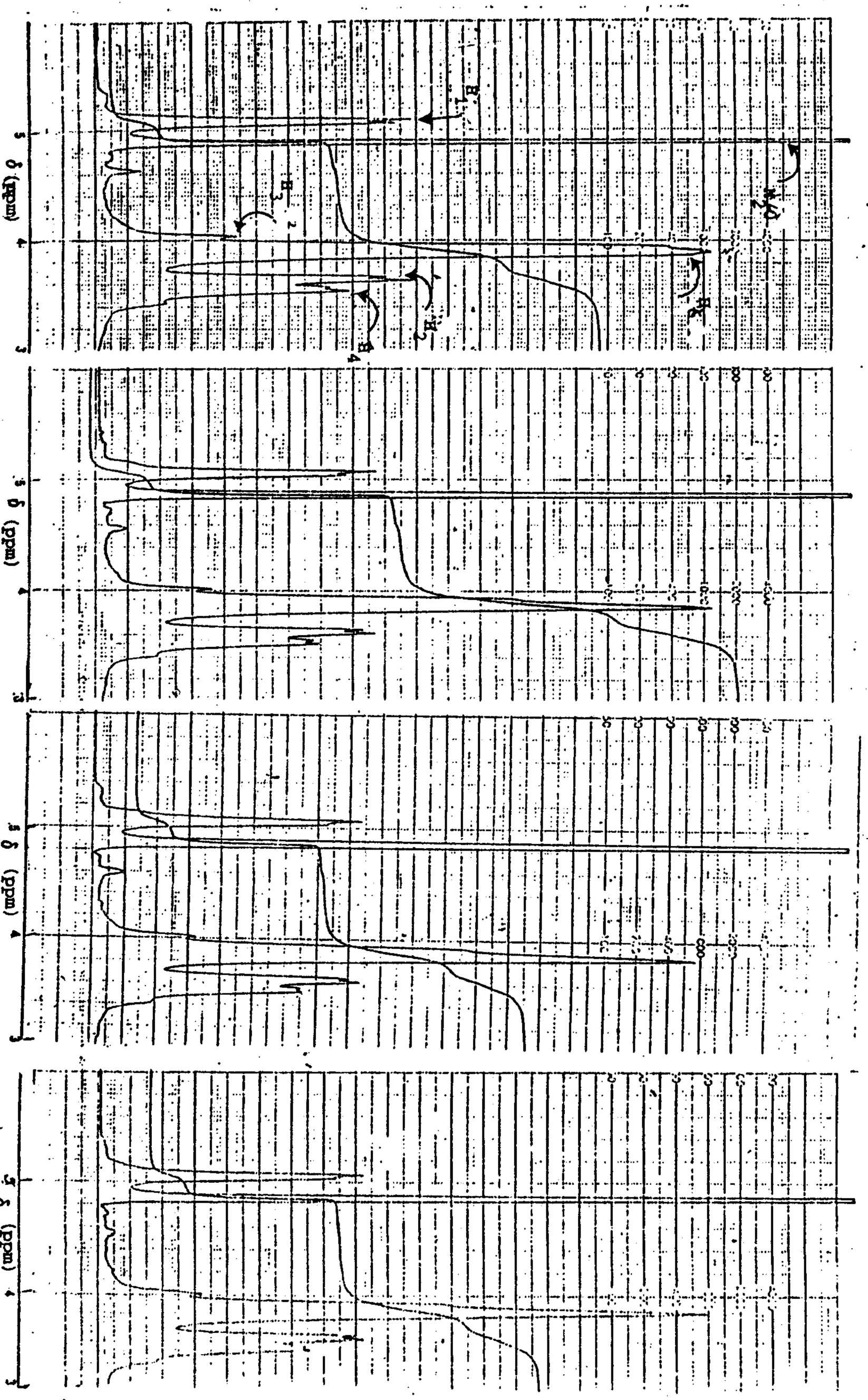

Fig. 1 : ^{1}H-NMR Spectra of γ-Cyclodextrin ($1x10^{-1}$M) Containing Various Amount of Piroxicam. Molar ratio of piroxicam-cyclodextrin: (A) 0.00, (B) 0.50, (C) 0.75, (D) 1.0 Solvent 0.2 N NaOD in D_2O.

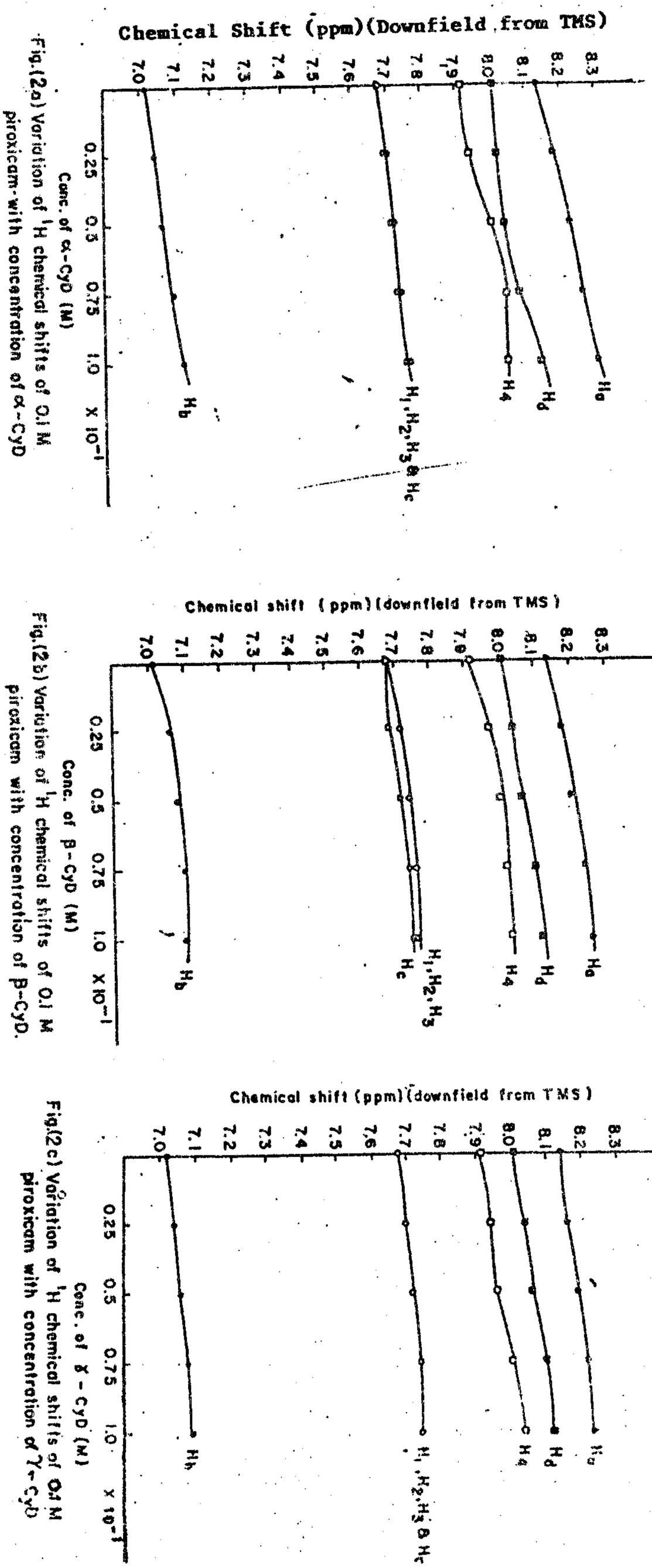

Fig.(2a) Variation of ^{1}H chemical shifts of 0.1 M piroxicam with concentration of α-CyD

Fig.(2b) Variation of ^{1}H chemical shifts of 0.1 M piroxicam with concentration of β-CyD.

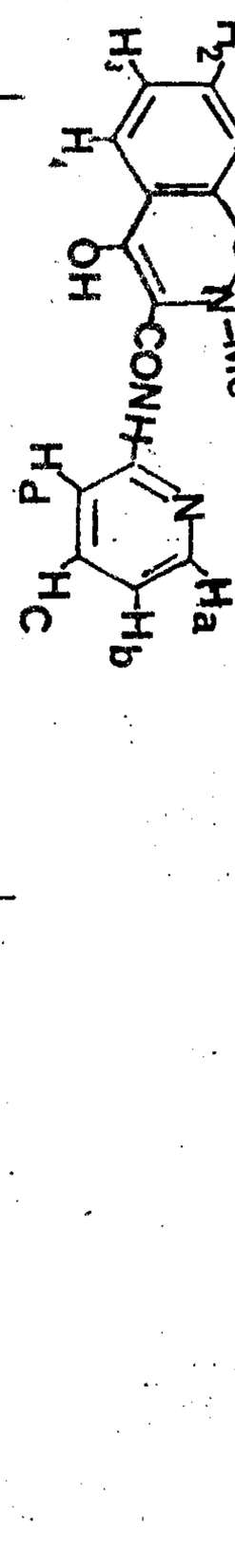

Fig.(2c) Variation of ^{1}H chemical shifts of 0.1 M piroxicam with concentration of γ-CyD

^{1}H-Nuclear Magnetic Resonance (NMR) Study of Piroxicam-Cyclodextrins Inclusion Complexes.

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استخدام الرنين النووى المغناطيسى فى التعرف على التركيب الاحتوائى لمركب البيروكسيكم مع السيكلودكستردين وأنواعه المختلفة

نبيل محمود عمر ـ عبدالحميد نجيب أحمد ـ هارويا ودا ـ سامية الحيزاوى

كلية الصيدلة ـ جامعة أسيوط ـ معهد العلوم الصيدلية ـ طوكيو ـ اليابان

فى هذا البحث تم فصل والتعرف على التفاعل الاحتوائى التركيبى لمركب البيروكسيكم مع السيكلودكسترين بأنواعه الثلاثة :
(الفا ـ بيتا ـ جاما) .

وقد تم التعرف على التكوين الاحتوائى عن طريق استخدام الرنين النووى المغناطيسى .

وفى هذا البحث تم استخدام طرق مختلفة لفصل التركيب الاحتوائى فى صورته الصلبة وقد تم عمل علاقة بين التركيزات المختلفة من البيروكسيكم والسيكلودكسترين بأنواعه المختلفة وأثرها فى التغيير النووى المغناطيسى للمركبات المختلفة .

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