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**ASSIGNMENT OF METHOXYL RESONANCES AND
OBSERVATION OF RESTRICTED ROTATION OF B-RING
OF 2'-METHOXY FLAVONES BY 2D-NOESY IN
CONJUNCTION WITH ASIS**

Key Words: ASIS and 2D-NOESY, assignment of methoxyl resonances, isoracemoflavone dimethyl ether, isocycloartocarpesin trimethyl ether and cycloartocarpesin trimethyl ether, hindered rotation of B-ring in 2',4'-disubstituted flavones

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ABSTRACT: 2D-NOESY in conjunction with aromatic solvent induced shifts (ASIS) allowed unequivocal assignments of methoxyl resonances in polymethoxylated pyranoflavones thus providing an additional aid for the structural elucidation of natural products.

In addition, the unusual nOe interactions observed in 2'-substituted B-ring flavones with H-3 or H-4" of the pyran ring suggested hindered rotation of the B-ring.

INTRODUCTION

Hydroxyl and methoxyl groups are ubiquitous in natural products. Various color reactions and spectroscopic methods have been extensively used for the location of hydroxyl groups^{1,2}. However comparative stability of C-O-CH₃ bonds do not allow application of similar techniques for the assignment of the methoxyl groups. We report here a direct method for precise assignments of methoxyl resonances in polymethoxylated compounds using 2D-NOESY in conjunction with aromatic solvent induced shifts (ASIS). These assignments provide additional aid for structure elucidation. Three closely related pyranoflavones *viz.* isoracemo-flavone dimethyl ether (1), cycloartocarpesin trimethyl ether (2) and isocycloartocarpesin trimethyl ether (3), synthesized by unambiguous routes^{3,4} were selected as models to illustrate the utility of the combined techniques⁵.

RESULTS AND DISCUSSIONS

NMR spectroscopy has limited scope for the assignment of methoxyl resonances due to lack of scalar couplings and close chemical shifts. Although empirical, ASIS studies have been used in limited number of cases^{6,7}. Understandably, unambiguous assignments of methoxyl resonances have so far eluded chemists. We felt that nOe interactions of the methoxyls with the proximal protons if any, would furnish useful structural informations. However, often closeness of chemical shifts of the methoxyl

protons may not allow to observe the individual nOe interactions. We felt that this problem could probably be circumvented by utilizing the differential shifts of methoxyl signals by aromatic solvents followed by the 2D-NOESY spectral studies. The utility of these combined techniques (NOESY and ASIS) has been illustrated by the following three examples.

The 2D-NOESY spectrum (FIG. 1) of isoracemoflavone dimethyl ether (1) in $CDCl_3$, showed expected interactions for 2,2-dimethyl pyran ring [δ 1.48 (gem dimethyl) «--» 5.72 (H-3'') «--» 6.74 (H-4'')]; 3',4'- dimethoxylated B-ring [7.49 (H-6') «--» 6.97 (H-5') «--» OMe, 7.32 (H-2') «--» OMe] and H-3 proton [6.57 (H-3) «--» 7.32 (H-2') and 7.49 (H-6')] (Table 1). The interaction of H-3 with both the protons (H-2' and H-6') is expected for the freely rotating B-ring. The resonances for protons of three methoxyl groups as well as H-4'' and H-8 did not resolve, thus it was not possible to observe their individual nOe interactions. However, these resonances appeared as well segregated signals when the spectrum was recorded in a mixture of $CDCl_3$ and C_6D_6 . 2D-NOESY was therefore recorded in the mixed solvents (FIG. 2). Based on the respective nOe 's the resonances at δ 1.25, 5.30 and 6.74 were attributed to gem dimethyl, H-3'' and H-4'' of the 2,2-dimethyl pyran ring, while the resonances at δ 6.43, 7.05 and 7.23 were ascribed to H-5', H-2' and H-6' protons of the B-ring (Table 1). The H-4'' doublet at δ 6.74 showed a clear interaction with the methoxyl signal at δ 3.94, thus the later resonance was attributed to C-5 methoxyl⁸. The methoxyl resonances at δ 3.33 and 3.38 showed interactions with δ 6.43 (H-5') and δ 7.05 (H-2') were assigned positions 4' and 3' respectively. Thus precise

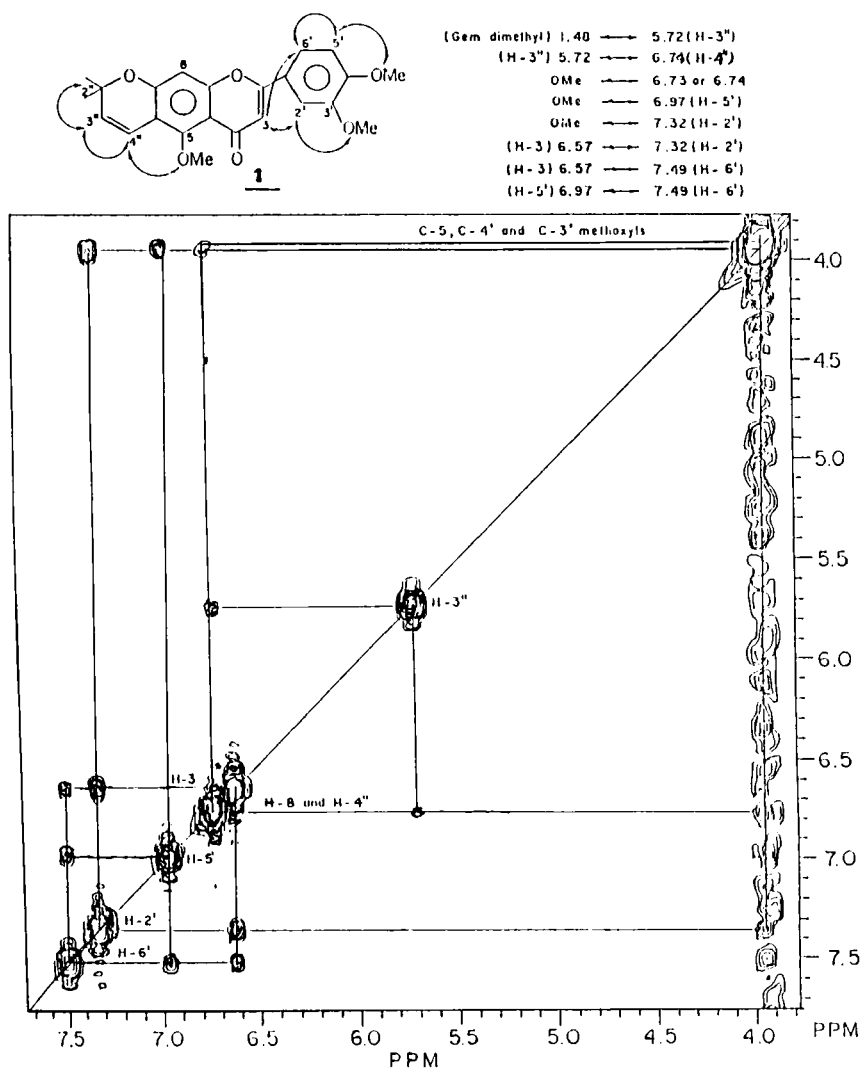


FIG. 1. Symmetrized NOESY Spectrum of Isoracemo-flavone Dimethyl Ether (**1**) in CDCl_3 .

TABLE 1
¹H NMR Data of Pyranoflavones (1-3) in CDCl₃ and CDCl₃ + C₆D₆.

| Protons | Compound 1 | | Compound 2 | | Compound 3 | |
|------------------|---|---|---|---|---|---|
| | CDCl ₃ | CDCl ₃ + C ₆ D ₆ | CDCl ₃ | CDCl ₃ + C ₆ D ₆ | CDCl ₃ | CDCl ₃ + C ₆ D ₆ |
| Gem dimethyl | 1.48 | 1.25 | 1.46 | 1.20 | 1.49 | 1.25 |
| H-3" | 5.72 | 5.30 | 5.67 | 5.32 | 5.58 | 5.30 |
| H-4" | 6.74 | 6.74 | 6.74 | 6.70 | 6.80 | 6.86 |
| H-2' | 7.32 | 7.05 | - | - | - | - |
| H-3' | - | - | 6.54 | 6.22 | 6.55 | 6.28 |
| H-5' | 6.97 | 6.43 | 6.60 | 6.31 | 6.61 | 6.34 |
| H-6' | 7.49 | 7.23 | 7.76 | 7.66 | 7.81 | 7.56 |
| H-3 | 6.57 | 6.65 | 6.85 | 7.12 | 6.95 | 7.06 |
| H-6 | - | - | - | - | 6.30 | 6.20 |
| H-8 | 6.73 | 6.67 | 6.63 | 6.65 | - | - |
| C-5 OMe | $\left\{ \begin{array}{l} 3.92 \\ \text{to} \\ 3.96 \end{array} \right\}$ | 3.94 | $\left\{ \begin{array}{l} 3.87 \\ \text{to} \\ 3.92 \end{array} \right\}$ | 3.88 | $\left\{ \begin{array}{l} 3.87 \\ \text{to} \\ 3.93 \end{array} \right\}$ | 3.32 |
| C-4' OMe | | 3.33 | | 3.34 | | 3.23 |
| C-2' or C-3' OMe | | 3.38 | | 3.21 | | 3.15 |

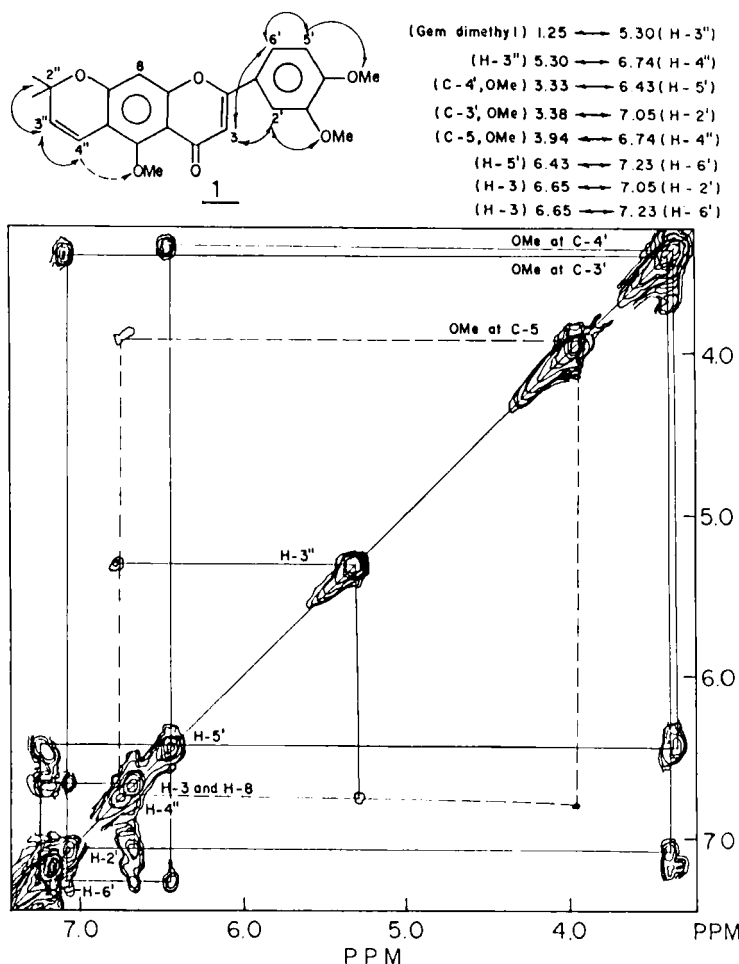


FIG. 2. NOESY Spectrum of Isoracemoflavone Dimethyl Ether (**1**) in $\text{CDCl}_3 + \text{C}_6\text{D}_6$.

assignments of all the methoxyl resonances were possible by the use of combined techniques (Table 1).

The NOESY spectrum (FIG. 3) of cycloartocarpesin trimethyl ether (**2**) in CDCl_3 revealed expected interactions of 2,2-dimethyl pyran ring and B-ring protons. The noteworthy feature of the

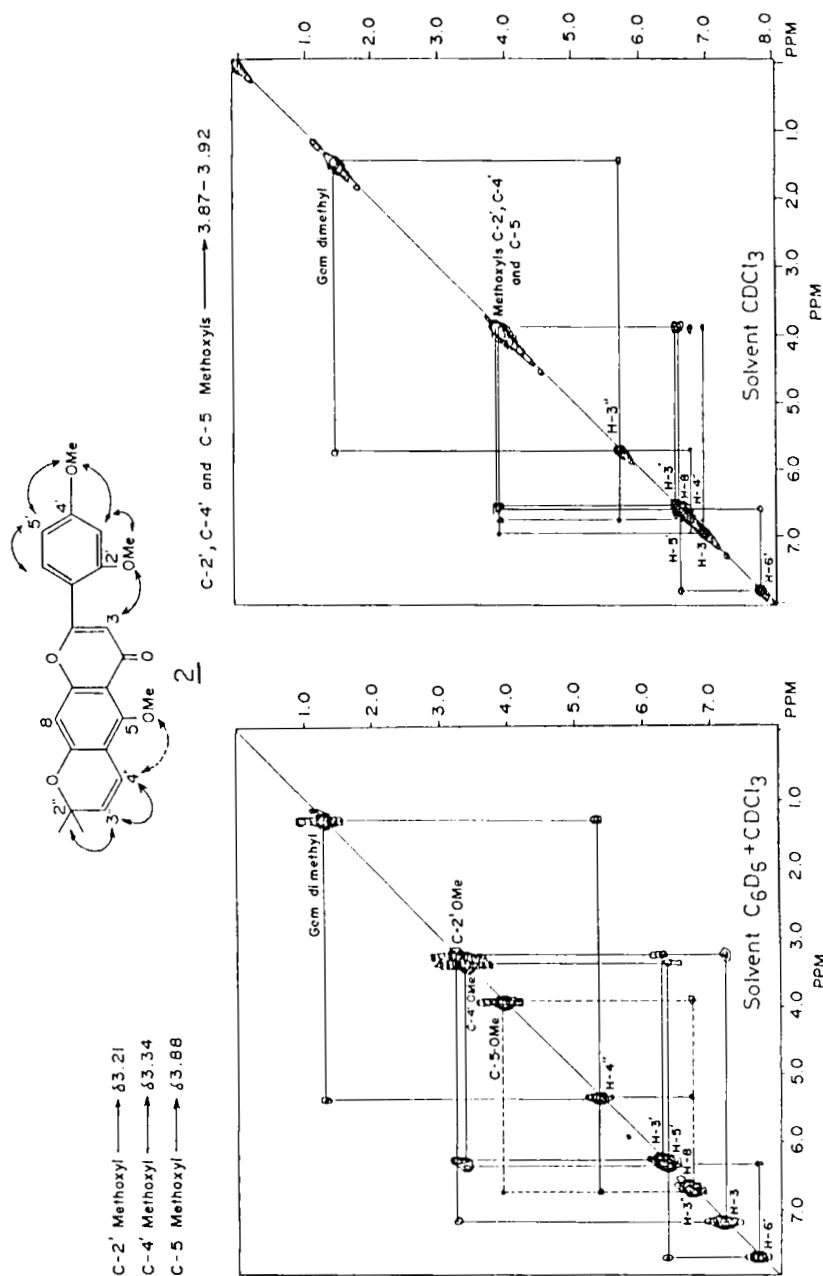


FIG. 3. Symmetrized NOESY Spectrum of Cycloartocarpin Trimethyl Ether (2) in $CDCl_3$ and $CDCl_3$ + C_6D_6 .

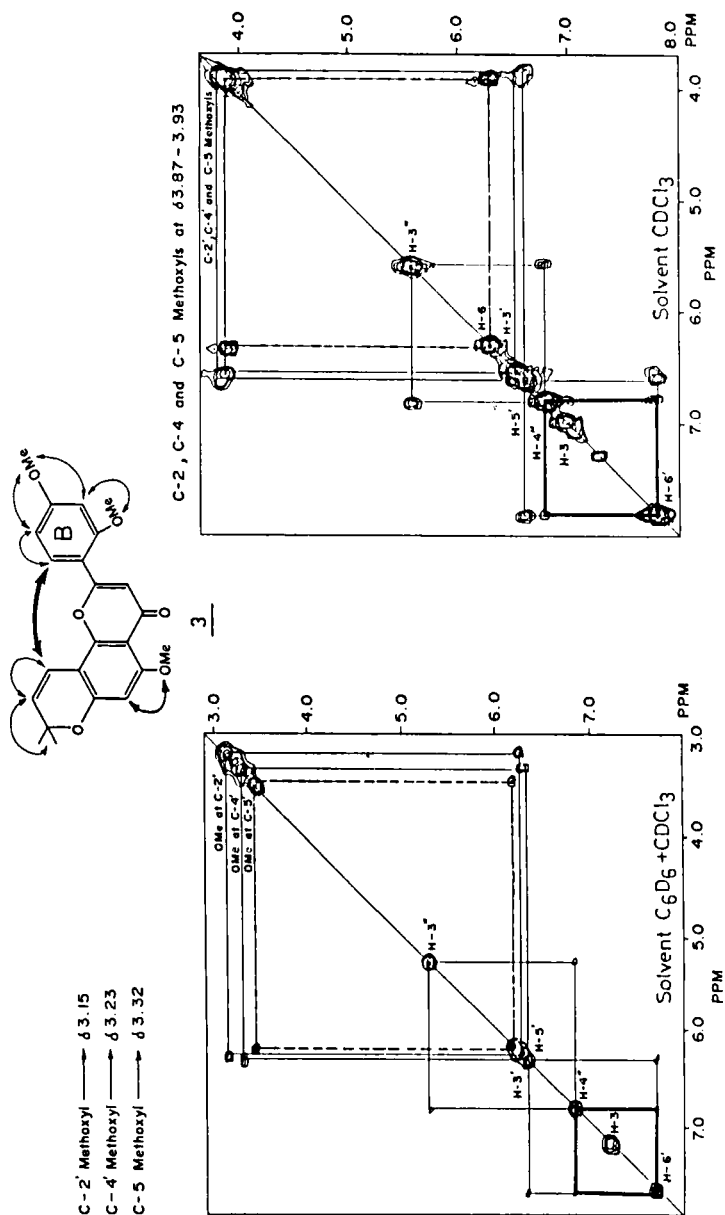


FIG. 4. Symmetrized NOESY Spectrum of Isocycloartocarpin Trimethyl Ether (**3**) in CDCl_3 and $\text{CDCl}_3 + \text{C}_6\text{D}_6$.

spectrum was that H-3 proton (δ 6.85) showed cross peak with methoxyl(s) only without any further interaction with H-6'. These interactions suggest hindrance in the rotation of the 2',4'-disubstituted B-ring possibly due to the steric factor exerted by the 2'-methoxyl group. The confirmation of involvement of 2'-methoxyl was obtained by NOESY spectral studies in mixed solvents (FIG. 3) The methoxyl resonances resolved distinctly at δ 3.21, 3.34 and 3.88 and were attributed to positions C-2', C-4' and C-5 respectively on the basis of their individual nOe interactions as discussed above (Table 1). A clear interaction between H-3 and 2'-methoxyl protons was observed while no interaction was observed between H-3 and H-6'; this further supports that there is restriction in rotation of the B-ring.

The NOESY spectrum (FIG. 4) of isocycloartocarpesin trimethyl ether (3) in CDCl_3 showed interactions of 2,2-dimethyl pyran ring, H-6 and B-ring protons^a. Unlike in the earlier two cases (compounds 1 and 2), the H-3 proton of compound 3 did not show any nOe interaction with either H-6' and/or methoxyl(s). Instead, an unusual nOe interaction between H-6' and H-4" was observed. In order to explain this, 2',4'-dimethoxyaryl ring has to be placed at right angle to the pyrone ring. 2D-NOESY spectrum in mixed solvents allowed assignment of methoxyl resonances at δ 3.15, 3.23 and 3.32 to positions C-2', C-4' and C-5 respectively on the basis of their individual nOe interactions (Table 1).

CONCLUSIONS

The combination of ASIS and 2D-NOESY provides a novel method for precise assignments of methoxyl resonances, thus increasing

the armory of the chemists for elucidation of structures of methoxylated products. As a result of these investigations on 1-3, it has been possible to distinguish 2',4'-dimethoxy phenyl from 3',4' dimethoxy phenyl (both having same ABX spin systems). In compound 2, nOe between H-3 and 2'-methoxyl proton suggests restriction in the rotation of the aryl side chain. In addition, unique nOe interaction between H-4" of the pyran ring with H-6' of B-ring was also observed in 3..

EXPERIMENTAL

Compounds 1, 2 and 3 were synthesized by the unambiguous route and their structures were established by physical and spectral data ^{3,4}. The 2D-NOESY spectra were recorded on a Bruker AM 500 FT-NMR spectrometer in CDCl₃ and mixed solvents (CDCl₃ and C₆D₆ in 1:2; v/v). NOESY experiments were performed with 256 t₁ and 1K t₂ points. The mixing time τ_m was 1 sec. The time domain data were zero filled to 512 points along t₁ axis. The data were multiplied by sine square bell and sine bell window functions along the t₂ and t₁ axes respectively, prior to respective Fourier transformations. Digital resolution in all the spectra is 15 Hz/point along with ω_1 and ω_2 axes. Absolute value spectra have been presented.

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