Elucidation of chemo- and regioselectivity in the alkylation of 6-methyl uracil using GIAO/^{13}C NMR

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Introduction:

Uracil is an interesting heterocyclic compound with few reactive centers which makes its alkylation reactions interesting from the viewpoint of chemo- and regioselectivity. The aim of this paper is to demonstrate the application of GIAO/^{13}C NMR chemical shifts for confirming the expected chemo- and regioselectivity of the alkylation of 6-methyl uracil.

Methods:

All the structures (Fig 1) were fully optimized with the GAUSSIAN G09 program at the B3LYP/6-31+G(d,p) theoretical level in the gas phase and Harmonic vibrational frequencies were evaluated at the same level in order to confirm the nature of the stationary points found.

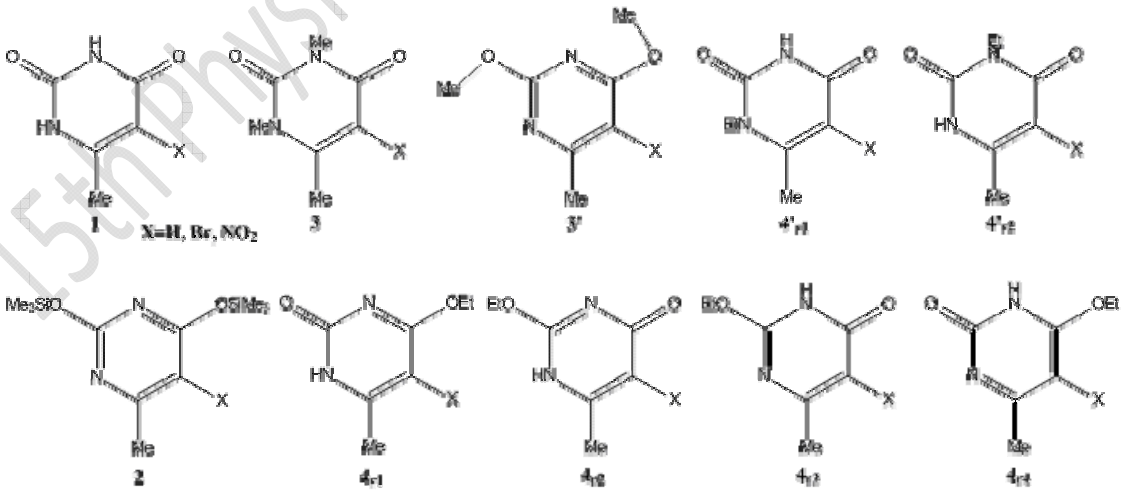

Fig 1: Structures of studied compounds

After the optimization, ^{13}C isotropic shielding were calculated with GIAO method [1] at the mPW1PW91/6-31+G(d,p) level, utilizing the PCM continuum method with UFF radii (acetone for X=NO_2 and chloroform for other compounds). The chemical shift relative to TMS for each nucleus in the molecule of interest (δ_i) is determined from the computed shielding constants computed for the same nucleus type in the reference compound (σ_{ref}), the computed shielding constants for each nucleus in the molecule of interest (σ_i), and the known experimental chemical shift for the reference compound (δ_{ref}) (see Eq. 1) [2]:

$$\delta_i = \sigma_{ref} - \sigma_i + \delta_{ref} \qquad (1)$$

Calculated chemical shifts are determined either using TMS as a single computational reference or using the second approach that was proposed recently [3], using methanol as the reference for sp^3-hybridized carbons and benzene for sp- and sp^2-hybridized carbons [the multi-standard (MSTD) approach]. Moreover, to evaluate the methods and the basis sets for prediction of calculated chemical shifts, this GIAO/^{13}C NMR procedure was employed for six major isomers at B3LYP/6-31+G(d,p) and mPW1PW91/6-311+G(2d,p) levels of theory. To reduce systematic errors, we use empirical scaling in this work, derived from linear regression analysis. Empirically scaled calculated chemical shifts are computed according to Eq. 2:

$$\delta_{scaled} = (\delta_{calc} - b) / m \qquad (2)$$

Where m and b are the slope and intercept resulting from a regression calculation on a plot of δ_{calc} against δ_{exp}.

Results and discussion:

According to calculated and experimental ^{13}C chemical shifts of carbons attached to N or O atoms, the chemo selectivity of studied reactions can be rationalized as follows:

1) In reaction of (1) with HMDS, O- silylation is preferred over N- silylation.
2) In reaction (2) with methyl iodide, N- methylation is preferred.
3) In reaction (2) with ethyl iodide, O- ethylation is preferred.

To study the regioselectivity, the difference between calculated and experimental ^{13}C NMR chemical shifts for all regioisomers of each compound shows that 4_{r1} is the preferred regioisomer.

Our study shows that the mPW1PW91 is a better hybrid functional than B3LYP with same basis set and surprisingly, a larger basis set 6-311+G(2d,p) has a grater mean absolute deviation (MAD) relative to standard basis set 6-31+G(d,p) (especially unscaled values).

Conclusions:

GIAO/^{13}C NMR chemical shifts with the mPW1PW91/6-31+G(d,p) level provides a powerful tool in the study of chemo- and regioselectivity problems in organic chemistry.

Reference:

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