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.

![Structures of studied compounds](image)

**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 ($\delta_i$) is determined from the computed shielding constants computed for the same nucleus type in the reference compound ($\sigma_{ref}$), the computed shielding constants for each nucleus in the molecule of interest ($\sigma_i$), and the known experimental chemical shift for the reference compound ($\delta_{ref}$) (see Eq. 1) [2]:

$$\delta_i = \sigma_{ref} - \sigma_i + \delta_{ref}$$  \hspace{1cm} (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:

$$\delta_{scaled} = (\delta_{calc} - b) / m$$  \hspace{1cm} (2)

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

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$_{c1}$ 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/13C 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: