molecule. The simplest example is the stunning alteration of properties when molecules of water are changed to molecules of methanol, by substituting a hydrogen atom of water molecule with a methyl group (Fig. 1). Less surprising, perhaps, is the readily miscibility of water and methanol. Yet, methanol has not been made out of water via a mechanism involving a hydrogen substitution. The unique facet of the methyl group is its impact and leading role when attached to biological molecules, particularly DNA. The methyl group is believed to have played a major role in the dynamics and evolution of biomolecules (Nickels, 2012).

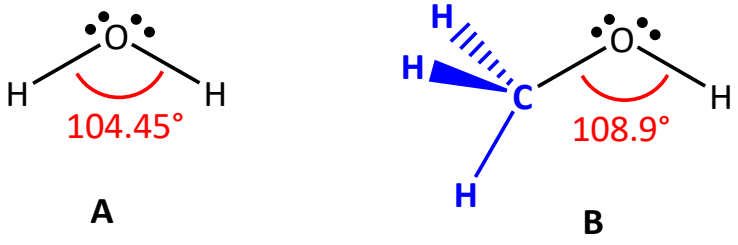


Figure 1. A – Water; **B** – Methanol

Indeed, the literature survey reveals a trove of reports on methylation of such molecules and the effects of thus-tethered methyl groups were illustrated[1)] (Barreiro et al., 2011). An astounding fact is the link between the methyl group in methylated DNA and the cancer development (Newberne & Rogers, 1986; Wajed et al., 2001); methylation of biological molecules contributes to the regulation of gene expression and protein function, and RNA processing. However, methylated flavones such as 5,7-dimethoxyflavone exhibit potent antiproliferative activities and inhibit the carcinogenic activation of some enzymes such as cytochrome P450 (Murakami et al., 2002; Morley et al., 2007). On the other hand, the impact of the methyl group on the biological potency of a drug has been broadly elucidated (Schönherr & Cernak, 2013). Although methamphetamine and amphetamine (Fig. 2) were generally claimed to present about the same drug potency, the methyl group in the methamphetamine renders amphetamine more lipid soluble, that is, increases its lipophilicity. Yet, methamphetamine was found to last longer because the methyl group decreases the polarity of the molecule, making the latter penetration easily into the blood (MacKenzie & Heischoner, 1997). Methionine, a sulfur- and methyl-containing amino acid, has been claimed to potentially detoxify a body from toxic heavy metals such as lead through methyl donating phenomenon (Chaitow, 1988); for this reason and others, L-methionine is taken as a dietary supplement.

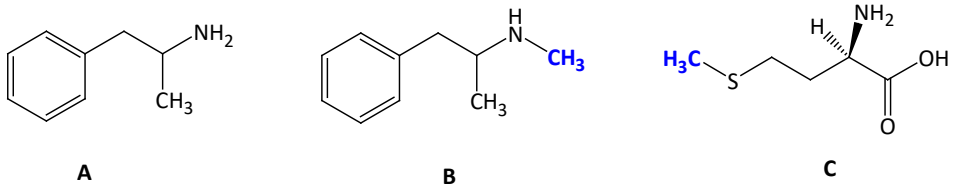


Figure 2. A – Amphetamine; **B** – Methamphetamine; **C** – L-Methionine

Because of its critical existence within some molecules, the term "methyl" usually preceded their common names, such as methyldopa (*antihypertensive drug)*, methyl orange (acid-base titration indicator), methyl red (acid-base titration indicator), methyl yellow (acid-base titration indicator), methyl green (cationic dye), methyl violet (cationic dye), and methyl viologen; the methyl groups in these substances are attached to nitrogen atoms. In general, the incorporation of methyl group onto an organic molecule is commonly achieved via a methylation reaction using a methylating agent. As per the site reactivity, the methylation may take place on the main atoms of the organic molecules, and, therefore one speaks chiefly of *C*-, *N*-, *S*-, and *O*-methylations. Screened literature revealed several methylating agents and a variety of catalysts to promote the methylation reaction (Lamoutreux & Agüero, 2009). The methylation of biological molecules occurs in the presence of enzymes as catalysts. Methylcobalamin (the cyano group in vitamin B12 is substituted by methyl group) is one of the biomethylating agents; it methylates heavy metals such as mercury.

Special effects/roles of methyl group

Besides the few above-cited effects and roles of the methyl group when present in biological molecules, other significant effects are worth of mentioning. Methyl fixation in drugs imparts some benefits for the healthcare and this was therefore associated with the coined term "magic methyl effect" (Barreiro et al., 2011; Schönherr & Cernak, 2013). For example, the enzymatic inhibiting effect of p38α (Fig. 3**A**) increased by 208 fold when methylated (Fig. 3**B**); IC_{50} of the unmethylated p38α was greater than 2500 nM, and that for the methylated one was ~12 nM (Angell et al., 2008). To one's surprise, the molecular structure of caffeine (Fig. 3**C**) differs from that of theobromine (Fig. 3**D**) by only an extra methyl group. The former is the main component of coffee, and the latter is that of cacao and chocolate. It seems that the extra methyl group on the caffeine molecule (coffee) has an active effect on one's central nervous systems, while theobromine (chocolate) smoothly affects one's muscle functions.[2)]

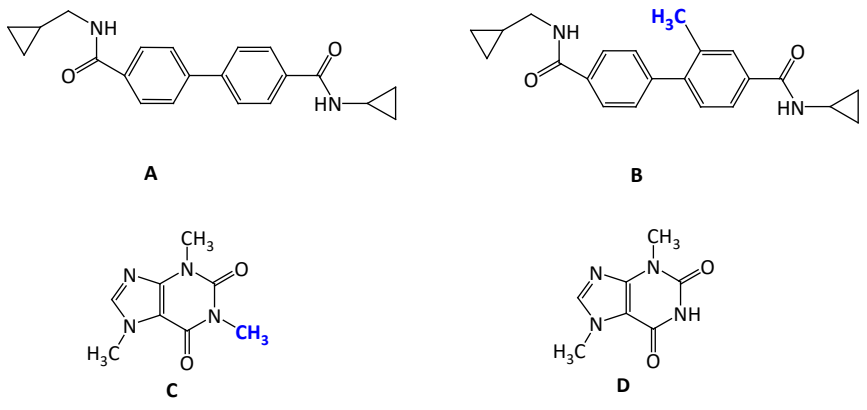
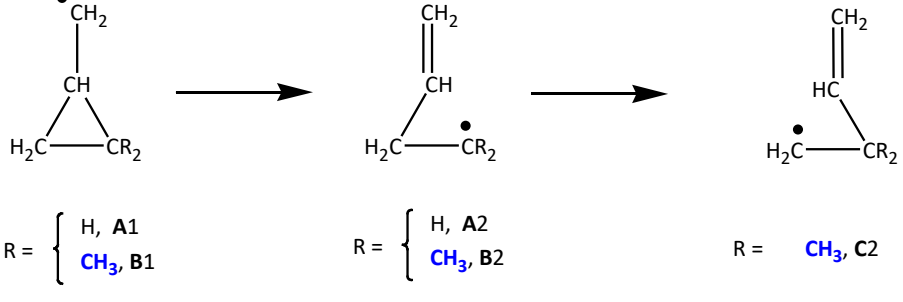


Figure 3. **A** – Pristine p38α; **B** – Methylated p38α; **C** – Caffeine; **D** – Theobromine

Yu and his co-workers (Li et al., 2006) demonstrated spectroscopically the contribution of methyl group in the formation of hydrogen bonding in DMSO-MeOH mixture. By means of quantum chemical calculations, methyl groups were shown to affect the strength H_2O---XF and H_2S---XF halogen-bonds (X = Cl and Br) (Li et al., 2010); O---X in H_2O---XF complex is stronger than S---X one in H_2S---XF complex but the reverse is true when hydrogen atoms are replaced with methyl groups. The calculated interaction energies (ΔE) suggest positive contribution of the methyl groups in the formation of halogen bonding: -16.5 kJ/mol for H_2O---ClF, -22.3 kJ/mol for $(CH_3)_2O$---ClF; -10.9 kJ/mol for H_2S---ClF, -27.2 kJ/mol for $(CH_3)_2S$---ClF. Based on theoretical calculations, Borden et al.(Zhang et al., 2011) advanced the effect of geminal methyl group on the rate of cyclopropylcarbinyl radical; the ring opening rate of **B**1 to 1,1-dimethyl-3-butenyl radical **B**2 should be 10^4 times faster than that of unsubstituted cyclopropylcarbinyl radical **A**1 to 3-butenyl radical (**A**2) and 10^6 times faster than that of **B**1 to 2,2-dimethyl-3-butenyl radical **C**2 (Scheme 1).



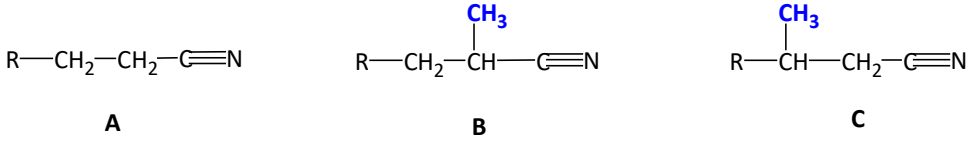
Scheme 1. Methyl effect on ring opening of cyclopropylcarbinyl radical

Valadbeigi & Gal (2016) disclosed the effect of the number of methyl groups on polarizabilities and dipole moments of oxygen-, nitrogen-, and phosphorus-containing molecules. That is, the polarizabilities increase linearly with the number of methyl groups, and the dipole moments either decrease or increase. It was found that the polarizabilities of H_2O, CH_2O, NH_3, and PH_3 increase by nearly 1.89, 1.83, 1.76, and 2.00 $Å^3$ per methyl group, respectively, when hydrogen atoms are substituted by methyl groups. In 1979, Burkert (1979) certified by means of molecular mechanics calculations the effects of the number of methyl groups on the geometry and conformational equilibrium of 1,3-dioxanes. Rao (2002) reported the effect of methyl groups on the chemical reactivity of isoxazoles as per the calculated π-electron densities, π-bond energies, delocalizing energies, and ionization potentials, which revealed a substantial electron exchange between isoxazole ring and the methyl groups. Russian workers Vdovin et al. (1973) proved the effect of the number of methyl groups and their positions on pyridine molecule on the pK_a and the nonlinear acoustic parameter (NLAP) as shown in Table 1.

Table 1. Effect of methyl groups on pyridine molecule

	Pyridine	α-Picoline	β-Picoline	Y-Picoline	2,3-Lutidine	2,4-Lutidine	2,6-Lutidine
pK_a	5.22	5.94	5.65	6.03	6.58	6.65	6.75
NLAP	1.000	1.135	1.079	1.149	1.263	1.270	1.281

The influence of methyl group on the fragrance of aliphatic nitriles (Fig. 4) was disclosed by Sell & Cairns (1982). The odor alteration was dependent not only on methyl substitution, but also on its position and on the length of the alkyl chains (Table 2).



A **B** **C**

Figure 4. A – Alkanonitrile; **B** – 2-Methyl alkanonitrile; **C** – 3-Methyl alkanonitrile

Table 2. Effect of methyl groups and the length of alkyl chain on the odor of alkanonitriles

	Octanonitrile	Nonanonitrile	Decanonitrile	Undecanonitrile	Dodecanonitrile
A	Peach and coconut notes	Peach notes stronger than those of A et coconut notes weaker than those of A	Waxy peach notes	Orange and mandarin notes	Orange character
B	Floral, jasminic character	Floral, jasminic, and peachy character	Floral, jasminic, and peachy character	Floral with lilac character	Floral with green jasminic character
C	Floral, jasminic character with agrumen quality	Floral, and jasminic, with green quality	Citrus floral notes	Green floral with slight citrus notes	Orange character, diffuse by green sea-fresh quality

Polo and his group (Müller et al., 2015) studied the influence of the methyl groups on phenanthroline ligands (Fig. 5) on the dye-sensitizing power of its ruthenium complex for solar cells. The incorporation of the ruthenium complex **B** in TiO_2 led to the following solar cell parameters: open-circuit potential, J_{SC} = 11.9 mA cm^{-2}; short circuit current density, V_{OC} = 0.627 V; overall performance, η = 5%; Fill factor, FF = 0.67. Those of unsubstituted ruthenium complex **A** were 13.25 mA cm^{-2}, 0.687 V, 6.1%, 0.67, respectively. The methyl groups were thus found to lower the sensitizer efficiency.

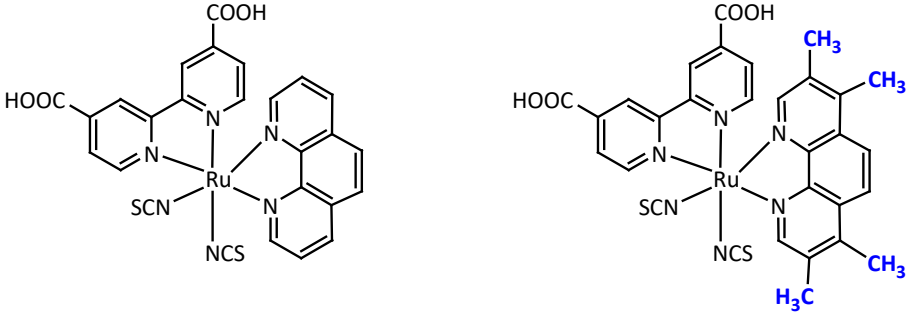
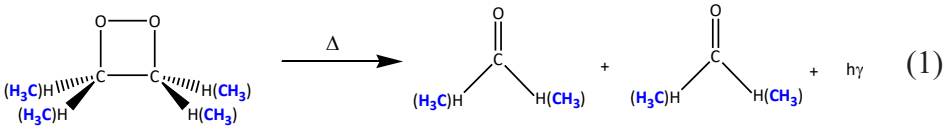


Figure 5. A – *cis*-[Ru(phen)($dcbH_2$)$(NCS)_2$]; **B** – *cis*-[Ru(($(CH_3)_4$-phen)($dcbH_2$)$(NCS)_2$]

Theoretical and experimental works have been undertaken to elucidate the chemiluminescence property of 1,2-dioxetanes[3] (O'Neal & Richardson, 1970; De Vico, 2007; da Silva & da Silva, 2014). Substitution by methyl groups in 1,2-dioxetane (Eq. 1) was shown to affect its thermal and chemiluminescent properties (Adam & Baader, 1985; Vacher, 2017); methylation promoted higher chemiluminescence yield. Higher number of methyl groups led to an increase in thermal stability; the tetramethyl-1,2-dioxetane was about 2.5 kcal/mol more thermally stable than the unsubstituted one. Also, the greater the number of methyl groups, the slower the dissociation of the dioxetane molecule, favoring higher population in triplet state from the ground one; the dissociation half-time $t_{1/2}$ for tetramethylated 1,2-dioxetane was nearly twice that for unmethylated one, 116.9 against 58.6 fs.



(1)

Removal of one of the methyl groups 7', 8', and 9' in abscisic acid (ABA) (Fig. 6**A**) resulted in modification of its physiologic activity (Walker-Simmons et al., 1994; Wilmer et al., 1998). While ABA was observed to induce a growth inhibition of oilseed rape embryos (*Brassica napus* L.) and an increase in the quantity of erucic acid, ABA demethylated at 7' showed a significant decrease in activity (Wilmer et al., 1998); however, the activity of ABA demethylated at 8' and 9' was less decreased. About the same results were found towards wheat embryo (*Triticumaestivum 1.*) (Walker-Simmons et al., 1994).

Ohno and his collaborators (Mukai et al., 2004) reported the impact of the methyl substituent on the liquid crystallinity and the ionic conductivity of *N*, *N*-dim ethylimidazoliumdodecylsulfonate (Fig. 6**B**). By increasing the number of methyl groups, the liquid crystallinity has the tendency to be annihilated; indeed, the fully methylated imidazolium salt showed no liquid crystalline phase. Peculiarly, the substitution at position 2 led to an imidazolium salt with no liquid crystallinity. *N*, *N*-dimethylimidazolium dodecylsulfonate presented an enantiotropicsmectic A phase, while 1,3,4-trimethylimidazolium salt showed monotropic phase.

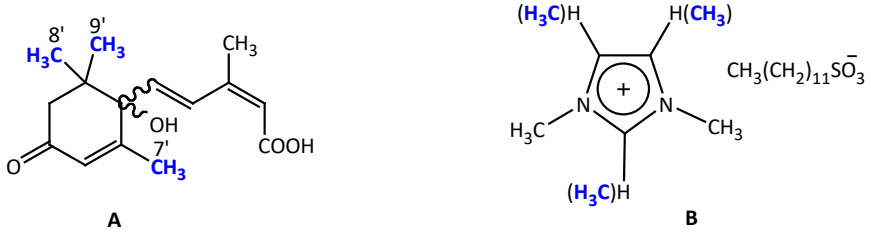


Figure 6. A – Abscisic acid; **B** – Methylated/unmethylated *N*, *N*-dimethylimidazolium dodecylsulfonate

The substitution of different carbon atoms of polyene chain of the retinal Schiff base by methyl groups affected its proton affinity, charge distribution, pK_a, and chromophore characteristic (Tajkhorshid & Suhai, 1999). Upon methylation, an increase in proton affinity of the Schiff base models could be ensued and the effect was more significant when substitution occurred at the even-numbered carbons atoms of the main chain, particularly at the terminal atom of the conjugated chain

Methyl groups on monocyclic aromatic hydrocarbons were demonstrated to reduce the formation of secondary organic aerosol (SOA), a particulate matter found in atmosphere and resulted from oxidation of organic molecules (Li et al., 2016); the SOA formation was in this order: benzene > toluene > *m*-xylene > 1,2,4-trimethylbenzene (pseudocumene) > pentamethylbenzene > hexamethylbenzene > 1,2,4,5-tetramethylbenzene. Methyl groups were believed to stabilize the ring-opening radical and to inhibit subsequently the formation of cyclic compounds and the oligomerization. The monocyclic aromatic hydrocarbon becomes less prone to oxidation as the number of methyl groups on the benzene ring increases.

Kim and his team (Park et al., 2013) studied the effect of the number of methyl groups in poly(styrene-*co*-sodium acrylate) ionomer (Fig. 7) on its mechanical properties and morphology. It was found that the matrix and cluster T_gs and ionic modulus E_{ionic} of **C** (ionomer with two methyl groups) were lower than those of **A** and **B** (ionomer with one methyl group).

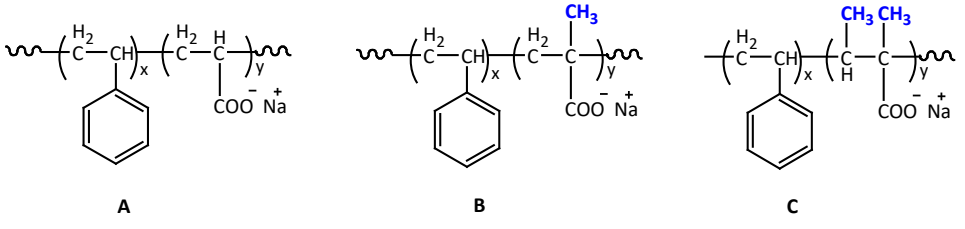
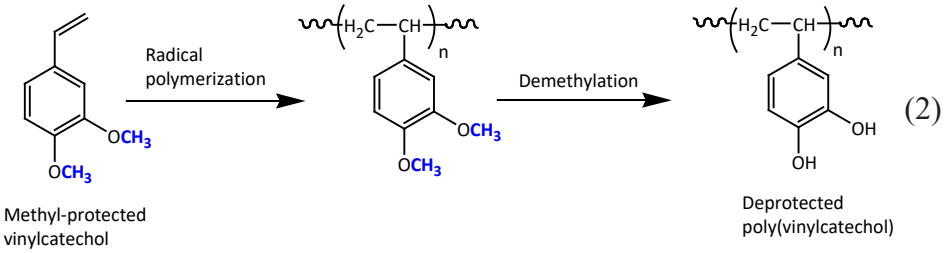


Figure 7. A – Poly(styrene-*co*-sodium acrylate) ionomer; **B** – Poly(styrene-*co*-sodium methacrylate) ionomer; **C** – Poly(styrene-*co*-sodium tiglate) ionomer

Methyl groups are sought for in the protection of some sensitive functional groups such as the phenolics, radical scavengers. For example, the radical polymerization of vinylcatechol does not proceed unless the hydroxyl groups are masked as traced in equation below (Eq. 2) (Daly & Moulay, 1986). A large number of demethylation agents, each with its demethylation specificity, were used to deprotect the phenolic functionality, and they are: BCl_3/DCM, Me_3SiI, HBr/NaI, HCl/

pyridine, EtSNa, LiCl/DMF, LiI/collidine, lithium diphenyl phosphide, $NiCl_2$/Zn, $BeCl_2$/alumina or KF/alumina,…etc. (Kulkarni et al., 1999).



(2)

NOTES

1. https://www.princeton.edu/chemistry/macmillan/group-meetings/PZ_MME.pdf
2. https://scienceandfooducla.wordpress.com/2015/09/29/caffeine-vs-chocolate-a-mighty-methyl-group/
3. http://uu.diva-portal.org/smash/get/diva2:1130597/FULLTEXT01.pdf

REFERENCES

Adam, W. & Baader, W.J. (1985). Effects of methylation on the thermal stability and chemiluminescence properties of 1,2-dioxetanes. *J. Amer. Chem. Soc.*, *107*, 410 – 416.

Angell, R., Aston, N.M., Bamborough, P., Buckton, J.B., Cockerill, S., deBoeck, S.J., Edwards, C.D., Holmes, D.S., Jones, K.L., Laine, D.I., Patel, S., Smee, P.A., Smith, K.J., Somers , D.O. & Walker, A.L. (2008). *Bioorg. Med. Chem. Lett.*, *18*, 4428 – 4432.

Barreiro, E.J., Kümmerle, A.E. & Fraga, C.A.M. (2011). The methylation effect in medicinal chemistry. *Chem. Rev.*, *111*, 5215 – 5246.

Burkert, U. (1979). Effects of methyl groups on the geometry and conformational equilibrium of 1,3-dioxanes. *Tetrahedron*, *35*, 691 – 695.

Chaitow L. (1988). *Amino acids in therapy: a guide to the therapeutic application of protein constituents*. Vermont: Healing Arts Press.

Daly, W.H. & Moulay, S. (1986). Synthesis of poly(vinylcatechols). *J. Polym. Sci. Polym. Symp.*, *74*, 227 – 242.

Da Silva, L.P. & Da Silva, J.C.G.E. (2014). Effects of methylation on the stability of dioxetanes: a theoretical analysis. *Sci. Lett. J.*, *3*, 63 – 66.

De Vico,L., Liu,Y.-J., Krogh, J.W. & Lindh, R. (2007). Chemiluminescence of 1,2-dioxetane: reaction mechanism uncovered. *J. Phys. Chem. A*, *111*, 8013 – 8019.

Dewick, P.M. (2006). *Essentials of organic chemistry: for students of pharmacy, medicinal chemistry and biological chemistry.* Chichester: John Wiley & Sons.

Exner, O. & Böhm, S. (2007). Substituent effects of the alkyl groups: polarity vs. polarizability. *Eur. J. Org. Chem. 2007*(17), 2870 – 2876.

Kulkarni, P.P., Kadam, A. J., Mane, R. B., Desai, U.V. & Wadgaonkar, P.P. (1999). Demethylation of methyl aryl ethers using pyridine hydrochloride in solvent-free conditions under microwave irradiation. *J. Chem. Res. (S)*, No. 6, 394 – 395. References therein.

Lamoureux, G. & Agüero, C. (2009). A comparison of several modern alkylating agents. *ARKIVOC., 2009*(1), 251 – 264.

Li, Q., Jing, B., Liu, Z., Li, W., Cheng ,J.,Gong, B. & Sun, J. (2010). Surprising enhancing effect of methyl group on the strength of O···XF and S···XF(X = Cl and Br) halogen bonds. *J. Chem. Phys.*, *133*, art. no. 114303.

Li, L., Tang, P., Nakao, S., Chen, C.-L. & Cocker III, D.R. (2016). Role of methyl group number on SOA formation from monocyclic aromatic hydrocarbons photooxidation under low-NOx conditions. *Atmos. Chem. Phys.*, *16*, 2255 – 2272.

Li, Q., Wu, G. & Yu, Z. (2006). The role of methyl groups in the formation of hydrogen bond in DMSO-methanol mixtures. *J. Amer. Chem. Soc.*, *128*, 1438 – 1439.

MacKenzie, R.G. & Heischober, B. (1997). Methamphetamine. *Pediatr. Rev.*, *18*, 305 – 309.

Morley, K.L., Ferguson, P.J. & Koropatnick, J. (2007). Tangeretin and nobiletin indice G1 cell cycle arrest but not apoptosis in human breast and colon cancer cells. *Cancer Lett.*, *251*, 168 – 178.

Mukai, T., Yoshio, M., Kato, T., Ohno, H. (2004). Effect of methyl groups onto imidazolium cation ring on liquid crystallinity and ionic conductivity of amphiphilic ionic liquids. *Chem. Lett.*, *33*, 1630 – 1631.

Müller, A.V., Mendonça, P.S., Parant, S., Duchanois, T., Gros, P.C., Beley, M. & Polo, A.S. (2015). Effects of methyl-substituted phenanthrolines on the performance of ruthenium (ii) dye-sensitizers. *J. Braz. Chem. Soc.*, *26*, 2224 – 2232.

Murakami, A., Koshimizu, K., Ohigashi, H., Kuwahara, S., Kuki, W., Takahashi, Y., Hosotani, K., Kawahara, S. & Matsuoka, Y. (2002). Characteristic rat tissue accumulation of nobiletin, a chemopreventive polymethoxylated flavonoid, in comparison with luteolin. *Biofactors*, *16* (3-4), 73 – 82.

Newberne, P.M. & Rogers, A.E. (1986). Labile methyl groups and the promotion of cancer. *Ann. Rev. Nutr.*, *6*, 407 – 432.

Nickels, J.D., Curtis, J.E., O'Neill, H. & Sokolov, A.P. (2012). Role of methyl groups in dynamics and evolution of biomolecules. *J. Biol. Phys.*, *38*, 497 – 505.

O'Neal, H.E. & Richardson, W.H. (1970). Thermochemistry of 1,2-dioxetane and its methylated derivatives: estimate of activation parameters. *J. Amer. Chem. Soc.*, *92*, 6553 – 6557.

Park, J.-J., Ko, K.-H., Song, J.-M. & Kim, J.-S. (2013). Effect of the number of methyl groups of the ionic repeat unit on thedynamic mechanical properties and morphology of poly(styrene-*co*-acrylate)-based ionomers. *Polymer*, *54*, 3914 – 3920.

Radom, L. (1975). Effects of alkyl groups on acidities and basicities in the gas phase: an *ab initio* molecular orbital study. *Aust. J. Chem.*, *28*, 1 – 6.

Rao, B.R. (2002). HMO Study on the effect of methyl group perturbations in isoxazoles. *Indian J. Chem*. Sect *B*, *41B*, 1694 – 1696.

Schönherr, H. & Cernak, T. (2013). Profound methyl effects in drug discovery and a call for new C-H methylation reactions. *Angew. Chem. Int. Ed.*, *52*, 12256 – 12267.

Sell, C.S. & Cairns, P. (1982). The influence of methyl groupsubstitution on the odour of aliphatic nitriles. *Perfumer & Flavorist, 7*, 14 – 16.

Tajkhorshid, E. & Suhai, S. (1999). Influence of the methyl groups on the structure, charge distribution, and proton affinity of the retinal Schiff base. *J. Phys. Chem. B*, *103*, 5581 – 5590.

Taft, RW. (1981). *Progress in physical organic chemistry*, *volume 13*. New York: John Wiley & Sons.

Vacher, M., Farahani, P., Valentini, A., Frutos, L.M., Karlsson, H.O., Galván, I.F. & Lindh, R. (2017). How do methyl groups enhance the triplet chemiexcitation yield of dioxetane?, *J. Phys. Chem. Lett.*, *8*, 3790 – 3794.

Valadbeigi, Y.& Gal, J.-F. (2016). Effect of the number of methyl groups on the cation affinity of oxygen, nitrogen, and phosphorus sites of Lewis bases. *J. Phys. Chem. A*, *120*, 9109 – 9116.

Vdovin, S.M., Ben'kovskii, V.G. & Nasibullina, L.S. (1973). Effect of the position and number of methyl groups on the acoustic parameters of mono- and dimethylpyridines and interrelationship between the reactivities and nonlinear properties. *Khim. Geterotsikl. Soedin.*, *3*, 356 – 358.

Wajed, S.A., Laird, P.W. & DeMeester, T.R. (2001). DNA methylation: an alternative pathway to cancer. *Ann. Surg.*, *234*, 10 – 20.

Walker-Simmons, M.K., Rose, P.A., Shaw, A.C. & Abrams, S.R. (1994). The 7'-methyl group of abscisic acid is critical for biological activity in wheat embryo germination. *Plant Physiol.*, *106*, 1279 – 1284.

Wilmer, J.A., Abrams, S.R., Helsper, J.P.F.G. & van der Plas, L.H.W. (1998). Role of the ring methyl groups in abscisic acid activity in erucic acid accumulation in oilseed rape (*Brassica napus* L.). *J. Plant Growth Regul.*, *17*, 19 – 23.

Zhang, X., Hrovat, D.A., Datta, A. & Borden,W.T. (2011). Effects of geminal methyl groups on the tunnelling rates in the ring opening of cyclopropylcarbinyl radical at cryogenic temperature. *Org. & Biomol. Chem.*, *9*, 3142 – 3145.

✉ **Prof. Saâd Moulay**
Laboratoire de Chimie-Physique Moléculaire et Macromoléculaire
Département de Génie des Procédés, Faculté de Technologie
Université Saâd Dahlab de Blida
B. P. 270, Route de Soumâa, 09000, Blida, Algeria
E-mail: polymchemlab@hotmail.com