

METHYL, THE SMALLEST ALKYL GROUP WITH STUNNING EFFECTS

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Abstract. In several instances, methyl group was found to play a pivotal role when present in a molecule. Its hydrophobic character has been the key success factor for specific performances when lipophilicity is the basic requirement for a phenomenon to occur. In some cases, chemical reactivity and physical phenomena are specifically linked to the effects of methyl group.

Keywords: caffeine; chemiluminescence; chocolate; fragrance; methyl; NLAP; SOA

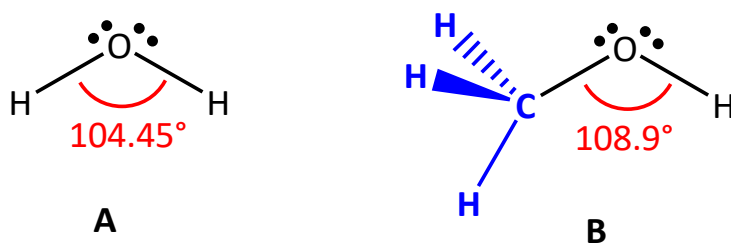
Introduction

Organic-related molecules (organic and organometallic ones) are often featured by the presence of groups that are actually assemblies of organic atoms. Of these are the functional groups, particularly the polyvalent ones, which peculiarly characterize the molecule and impart some of its characteristic chemical and physical properties. As the term ‘functional’ may suggest, the functional group would make the molecule chemically reactive and hence transformable. Functionalization of a molecule would bring about changes in its known properties which can be dependent on the intrinsic characteristics of the related functionalizing agent, such as polarity, spatial geometry and spatial volume.

Of particular interest, alkyl groups in an organic molecule present several effects, owing to their hydrocarbonaceous nature: electron induction, electron donation, hindrance, hyperconjugation, energy, hydrophobicity, polarizability...etc; moreover, these effects usually varied with the length of the alkyl chain, its linearity, and its degree of branching (Taft, 1981). The alkyl groups are known to lower the acidity of carboxylic acids and alcohols and the longer the alkyl chain, the higher the effect (Radom, 1975; Dewick, 2006). Besides, the polarity and the polarizability were demonstrated to explain the effects of the alkyl groups on the acidity and the basicity of alcohols, and the stability of cations and anions (Exner & Böhm, 2007). Another role of alkyl groups is their protection of some sensitive functional groups such as phenolics.

Methyl group, being the smallest alkyl group, has been the readily recourse when organophilic (lipophilic) character is sought for a water-borne

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).



Indeed, the literature survey reveals a trove of reports on methylation of such molecules and the effects of thus-tethered methyl groups were illustrated¹⁾ (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.

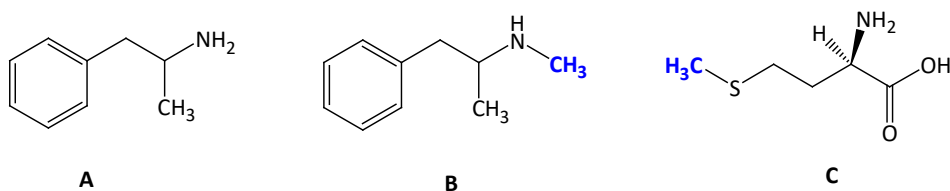


Figure 2. A – Amphetamine; B – Methamphetamine; C – L-Methionine

Because of its critical existence within some molecules, the term “methyl” usually preceded their common names, such as methyl dopa (*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 p38 α (Fig. 3A) increased by 208 fold when methylated (Fig. 3B); IC₅₀ of the unmethylated p38 α 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. 3C) differs from that of theobromine (Fig. 3D) 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⁾

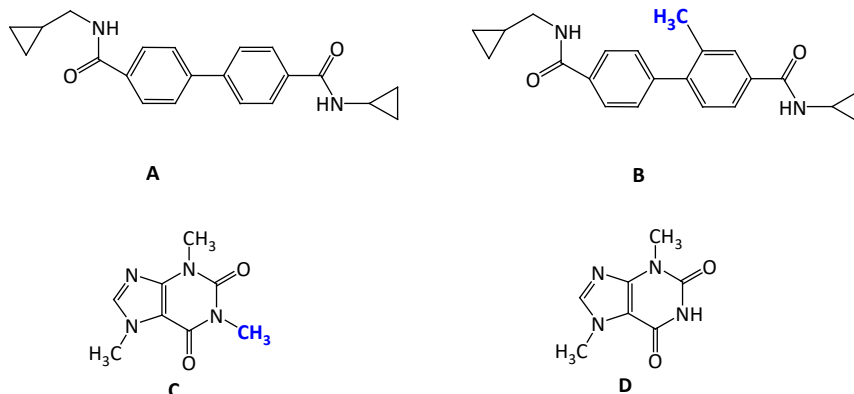
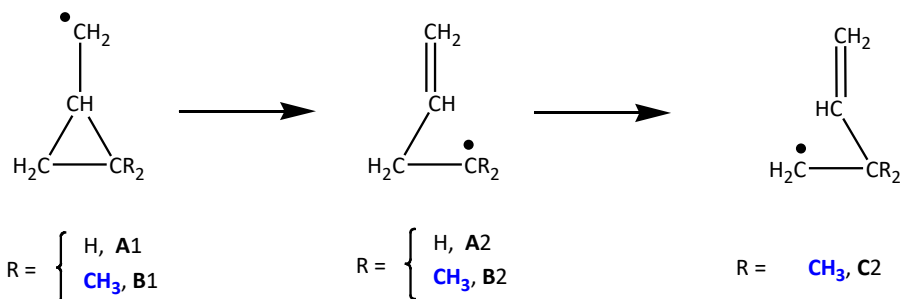


Figure 3. **A** – Pristine p38α; **B** – Methylated p38α; **C** – Caffeine; **D** – Theobromine

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 $\text{H}_2\text{O} \cdots \text{XF}$ and $\text{H}_2\text{S} \cdots \text{XF}$ halogen-bonds ($\text{X} = \text{Cl}$ and Br) (Li et al., 2010); $\text{O} \cdots \text{X}$ in $\text{H}_2\text{O} \cdots \text{XF}$ complex is stronger than $\text{S} \cdots \text{X}$ one in $\text{H}_2\text{S} \cdots \text{XF}$ 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 $\text{H}_2\text{O} \cdots \text{ClF}$, -22.3 kJ/mol for $(\text{CH}_3)_2\text{O} \cdots \text{ClF}$; -10.9 kJ/mol for $\text{H}_2\text{S} \cdots \text{ClF}$, -27.2 kJ/mol for $(\text{CH}_3)_2\text{S} \cdots \text{ClF}$. 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 **B1** to 1,1-dimethyl-3-butenyl radical **B2** should be 10^4 times faster than that of unsubstituted cyclopropylcarbinyl radical **A1** to 3-butenyl radical (**A2**) and 10^6 times faster than that of **B1** to 2,2-dimethyl-3-butenyl radical **C2** (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 $\text{\AA}^3$ 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 $\text{p}K_a$ 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	γ -Picoline	2,3-Lutidine	2,4-Lutidine	2,6-Lutidine
$\text{p}K_a$	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).

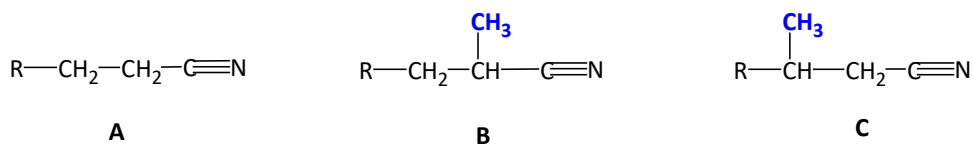
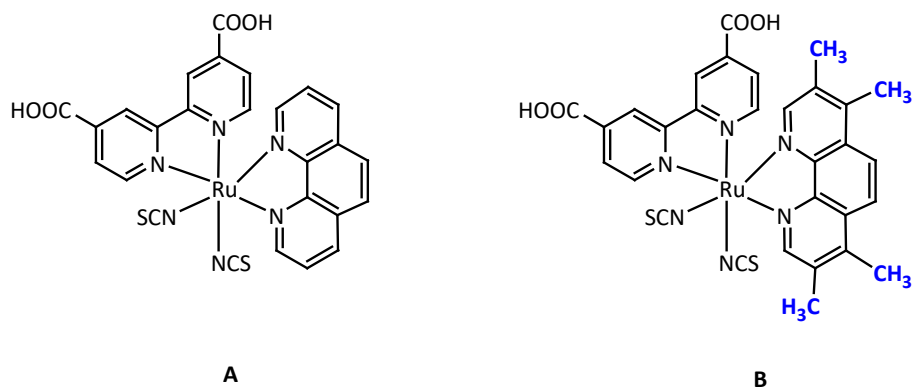


Figure 4. **A** – Alkanonitrile; **B** – 2-Methyl alkanonitrile; **C** – 3-Methyl alkanonitrile

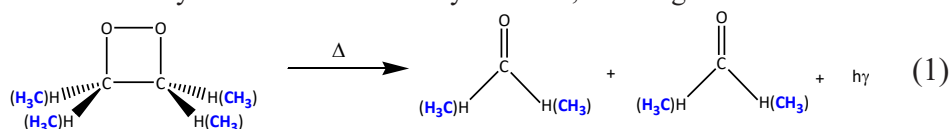
Table 2. Effect of methyl groups and the length of alkyl chain on the odor of alkanonitriles

	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, $J_{sc} = 11.9 \text{ mA cm}^{-2}$; short circuit current density, $V_{oc} = 0.627 \text{ V}$; overall performance, $\eta = 5\%$; 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** – $cis\text{-[Ru(phen)(dcbH}_2\text{)(NCS)}_2\text{]}$; **B** – $cis\text{-[Ru((CH}_3\text{)}_4\text{-phen)(dcbH}_2\text{)(NCS)}_2\text{]}$

Theoretical and experimental works have been undertaken to elucidate the chemiluminescence property of 1,2-dioxetanes³⁾ (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.



Removal of one of the methyl groups 7', 8', and 9' in abscisic acid (ABA) (Fig. 6A) 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 (*Triticum aestivum* L.) (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*-dimethylimidazoliumdodecylsulfonate (Fig. 6B). 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.

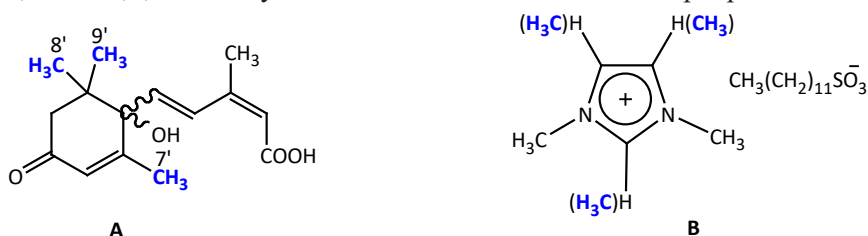


Figure 6. **A** – Abscisic acid; **B** – Methylated/unmethylated *N,N*-dimethylimidazolium dodecylsulfonate

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_g s 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).

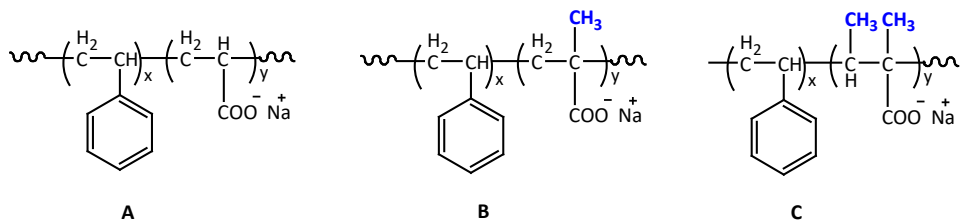
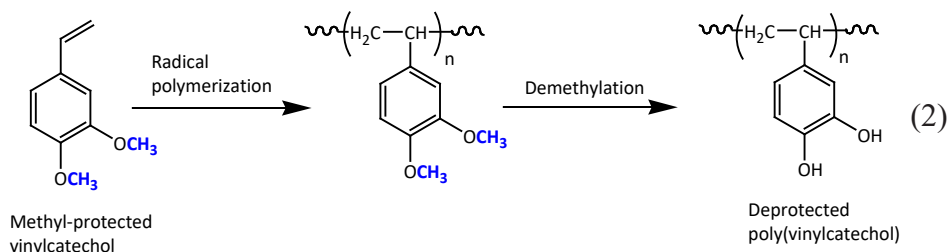


Figure 7. **A** – Poly(styrene-*co*-sodium acrylate) ionomer; **B** – Poly(styrene-*co*-sodium methacrylate) ionomer; **C** – Poly(styrene-*co*-sodium tiglate) ionomer

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, Lil/collidine, lithium diphenyl phosphide, NiCl_2/Zn , $\text{BeCl}_2/\text{alumina}$ or $\text{KF}/\text{alumina}$,...etc. (Kulkarni et al., 1999).



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>

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