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Molecular interactions between terpenoid mosquito repellents and human-secreted attractants

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ABSTRACT

Molecular interactions between terpenoid mosquito repellents and three typical human-secreted attractants, ammonia, 1-octen-3-ol, and formic acid were studied. Relative energies, bond distances, and bond angles of the molecular interactions were obtained at HF level to evaluate the interaction intensity and types. The effects of molecular interactions on repellency were investigated by the subsequent quantitative structure–activity relationship (QSAR) study. The results of this study suggest that attractant–repellent interaction should not be ignored and could be helpful for future research on the repelling mechanism of mosquito repellents.

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Mosquito repellents are a group of compounds which act to prevent humans from mosquito biting.[1] The spread of some fatal epidemic diseases,[2] like malaria, which caused 1.17 million deaths in 2010, are caused by mosquito biting.[3] Also, drug resistances become more common. For example, *Plasmodium falciparum* (Welch) has an increased resistance to anti-malarial drugs.[4] These exemplify the reason why mosquitoes are causing more and more health issues. Therefore, as a way to remedy this situation, repellent is recommended as a way for personal protection, and thus, the development of powerful mosquito repellents is extremely important. Traditional mosquito repellent screening processes are expensive and time-consuming. Quantitative structure–activity relationship (QSAR) has therefore been applied to assist with this process.[5] However, only a few studies have investigated the quantitative relationships between chemical structures of mosquito repellent and their repellency.[6–11]

Moreover, the repelling mechanism is still unclear and, to certain extents, controversial. The *N*,*N*-diethyl-3-methyl benzoyl amide (DEET), which was discovered in 1954,[12] has been one of the most successful mosquito repellents used for decades.[13] Numerous studies have been carried out in order to understand how this repellent works. Some researchers have confirmed that DEET can block electrophysiological responses of olfactory sensory neurons to attractive odors. Davis et al. found that DEET inhibits lactic acid-sensitive neurons, a pair of chemoreceptor neurons in the grooved-peg (A3) on the antennae of the mosquito, *Aedes aegypti*.[14] Recently, Ditzen et al. found that DEET strongly inhibited 1-octen-3-ol-evoked electrophysiological responses in *Anopheles gambiae* and *Drosophila melanogaster*.[15] Another opinion is that the mosquito evades its host after its olfactory neuron is activated by repellent DEET. Syed et al. identified an olfactory receptor neuron (ORN) housed in a trichoid sensillum on the *Culex quinquefasciatus* antennae that detects DEET in a dose-dependent manner. This means that the mosquito endows with DEET-detecting ORNs, to detect and avoid DEET.[16] Dogan et al.[17] found that DEET acts as an attractant when a human host is absent and a repellent in the presence of the host. Such observations are confusing and difficult to explain. It may imply that attractants from human hosts may affect some properties of 'commercial repellents' and the repelling mechanism could be much more complicated than what one would expect. The role of attractants from human hosts and their potential effect on the repelling mechanism have been ignored in most QSAR studies done so far.

It is known that, besides L-lactic acid, there are many attractant compounds from skin emanation, for example, ammonia, 1-octen-3-ol, and some short-chain carboxylic acids. Ammonia, ranging from 17 μg/L to 17 mg/L, makes a significant contribution to the

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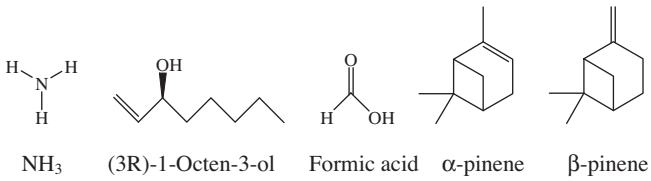


Scheme 1. Structures of three attractants, α-pinene and β-pinene.

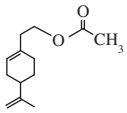
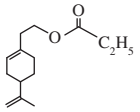
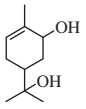
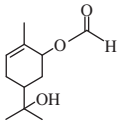
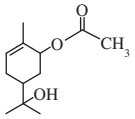
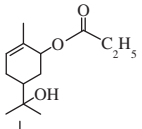
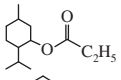
mosquito (*Aedes aegypti*) attraction behavior when placed together with lactic acid.[18] 1-octen-3-ol is believed to increase the attractiveness of L-lactic and CO_2 in field studies.[19] Bosch et al. found that C1–C3 and C5–C8 carboxylic acids, over a wide range of concentration, could enhance the attractiveness of lactic acid.[20] Furthermore, Cork et al. also observed that formic acids elicit the largest amplitude EAG response in the electroantennography (EAG) assay on *Anopheles gumbiae* Giles.[21] It is obvious that ammonia, 1-octen-3-ol, some short-chain carboxylic acids, and etc make humans attractive to mosquitoes. Recently, it was hypothesized that DEET may suppress the release of physiologically relevant compounds, such as the above attractants, after smeared on human skin. Meaning, DEET altered the chemical profile of emanations by a 'fixative' effect that may also contribute to repellency.[16] Unfortunately, more detail about the 'fixative' effect still remains mysterious. Because of the complicated roles of repellents and attractants, some preliminary studies have started to focus on what happens between the repellents and attractants and how they may affect the repellency.[22–26]

In this study, ammonia, 1-octen-3-ol, and formic acid were chosen as characteristic compounds from humans. To further understand these compounds, molecular interactions were investigated. Also, a group of terpenoid repellents as well as their effect on the mosquito repellency were studied. Theoretical calculations were performed to show how ammonia, 1-octen-3-ol, formic acid, and repellents interact between each other. Subsequent QSAR studies were used to elucidate how the complexes have an effect on the repellency.

22 Six-member-ring terpenoid mosquito repellent compounds were synthesized from α-pinene or β-pinene (Scheme 1). Their repellency against *Aedes albopictus* was tested. Structural information and repellency values of compounds were obtained from former studies[10,27], shown in Table 1.

Structures of three attractant molecules, twenty-two terpenoid mosquito repellents, and the attractant–repellent complexes were built and optimized using GaussView 4 and GAUSSIAN 03W software

Table 1
The interaction energy (in kJ/mol) calculated at HF level

No.	Formula of structure	LogCRR	NH_3-repellent	1-Octen-3-ol-repellent	Formic acid-repellent
1		1.767155866	−8.3	−15.8	−20.7
2		1.803457116	−15.3	−16.7	−21.0
3		1.861534411	−13.0	−8.6	−25.5
4		1.954242509	−10.3	−10.2	−23.1
5		1.908485019	−19.9	−10.5	−21.0
6		1.857332	−19.9	−14.0	−26.1
7		1.72427587	−14.1	−10.6	−19.6
8		1.587710965	−13.8	−16.8	−21.7
9		1.607455023	−14.7	−16.5	−19.0
10		1.838849091	−12.6	−10.5	−22.2

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