Вплив діамантильного замісника на реакційний центр карбонільних сполук

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Трет-бутильний та адамантильний замісники – стандартні об'ємні замісники, які використовуються в органічному синтезі для енантіоселективних пертво-рень. Наявність об'ємного замісника у субстраті підвищує діастереоселективність реакції, як це було показано для фотоциклізації та анізотропних перегрупувань. Такі групи також здатні стабілізувати такі нестабільні молекули, як триоксани та карбени. Наступним кроком логічно вважати збільшення розміру об'ємної групи. Молекулярний об'єм діамантану очевидно набагато більший за адамантан, при цьому слід мати на увазі топологічну різницю між 1- та 4- ізомерами (1-dAd та 4-dAd відповідно). Досить швидкий розвиток хімії діамондоїдів [1] та доступність різних похідних діамантану розкриває нові можливості для використання таких об'ємних замісників як діамантан у стереоконтрольованих синтезах. Було досліджено вплив діамонтанового замісника на реакційний центр експеримен-тально та теоретично. Комп'ютерні розра-хунки було проведено використовуючи методи DFT та DFT-D, з B3LYP, B97D та M062X функціоналами. Експериментальне дослідження було проведено через дослід-ження реакції Корі-Чайковського для діаман-тильних кетонів. Було показано, що на відстані двох CH$_2$ груп вплив каркасу є незначним. При цьому за відстані однієї CH$_2$ групи між реакційним центром та діамантаном, каркас перешкоджає sp^2-sp^3 переходу вуглецю. За відсутності CH$_2$ групи між діамантаном та реакційним центром, замісник перешкоджає доступу реагенту до карбонільної групи.

Steric Bulkness of Diamondoidyl Substituents

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The influence of the diamondoidyl substituent on the reaction center was investigated experimentally and computationally. Calculations were provided at DFT and DFT-D, using B3LYP, B97D and M062X functionals. Experimental investigation was made by studying the Corey-Chaykovsky reaction. The latter was explored with dimethylsulfoxonium methylide and diamondoidyl ketones, which has different distance between the carbonyl group and the cage. Diamondoidyl substituent was shown to have negligible effect on the reactive center within 2 CH$_2$ groups. While in ketones, bearing one CH$_2$ group between cage and carbonyl, it hampers tetrahedization of the reactive center. In case of methyl diamondoidyl ketones the cage hinders the access of the reagent.

**Key words** – diamondoids, DFT calculations, kinetics, reaction center.

I. Introduction

Tert-butyl (*t*Bu) and adamantyl (Ad) represent "standard" bulky groups that are widely used for stereocontrolled organic transformations. While the relative influence of tBu and Ad groups has been verified quantitatively on the example of 1-Ad, *t*Bu, 1-bicyclo[2.2.1]- octyl and 1-bicyclo[2.2.2]-heptyl, such analysis for dAd or higher diamondoidyls hasn't been provided yet. The molecular volume of dAd is markedly higher than that for Ad; additionally the topological divergence between the positional 1- and 4-isomers (1-dAd and 4-dAd, respectively) must be taken into account. Herein we present the combined quantitative experimental/computational study on the influence of Ad and 1-dAd, and 4-dAd groups on the reactivity of carbonyl group in Corey reaction, whose sensitivity towards steric effects is well-documented.

We vary the distance between the carbonyl group and the diamondoidyl group by the elongation of the carbon chain linking them in order to estimate the influence of the cage substituent on the reaction center.

II. Experimental investigation of the influence of the diamondoidyl substituent on the reaction center

As expected, ketones **1** and **4**, whose structures contain the most remoted cage moieties from the reaction center are most reactive and differ only slightly from each other (1.5 times). We conclude, that adamantyl substituent in **1** may cause larger steric hindrance than the diamantyl at larger distances.
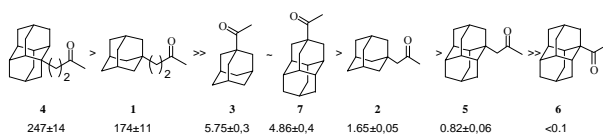
Scheme. 1. Rate constants for the ketones 1-7

In contrast, at shorter distances 1-diamantyl subsistent displays pronouncedly higher steric bulkiness than adamantyl group. The difference in reactivity **3** and **6** is remarkable: the diamantyl ketone **6** is inert towards DMSM even under prolonged heating, whereas adamantyl ketone **3** is moderately reactive (k=5.75•10^{-5} L^2/(mol^2*s)); the apical isomer **7** is nearly as reactive as adamantyl ketone **3** (k=5.7•10^{-5} and 4.9•10^{-5} L^2/(mol^2*s), respectively). Thus, opposite effect is observed for the influence of adamantine and diamantine cages at short and large distances to the reactions center. We observed unexpectedly low reactivity of ketone **2**, which is less reactive then **3**, following the general reactivity dependence: **1** (CH$_2$=2) > **3** (CH$_2$=0) > **2**(CH$_2$=1) in the adamatane ketone series. In contrast such a dependence for the respective diamantine ketones is normal, i.e.: **1** (CH$_2$=2) > **2** (CH$_2$=1) > **3**(CH$_2$=0). Such counterintuitive small rate constant, observed for ketone 2 needs comprehensive analysis and interpretation.

III. Computational investigation of the influence of the diamondoidyl substituent on the reaction center

We first analysed the importance of the entrance complexes in the reaction of ketones **1-6** with DMSM. In contrast to B3LYP, where the complexations of ketones is exergonic due to high exothermicities, the dispersion-corrected methods reveal high complexation endergo-nicities. This allows us to exclude formation of the initial clusters form the consideration.

Geometries of TS calculated at B3LYP, MO62X and B97D functionals are similar. We observed that barrier decreases on ~2 kcal/mol when oxygen of DMSM and carbonyl oxygen are in *trans* position. Moreover, for all model ketones syn TSs are more stable then anti on ~ 3 kcal/mol. *Syn-* or *anti-* TS are assigned to the relative position of ylide group and oxygen of the carbonyl group around the newly formed C-C bond. We provided calculations only for the TSs, as it was shown that addition of the ylide to the carbonyl is nonreversible and rate-determing,[60] for the reaction of the dimethyl-sulfonium benzylide with benzaldehyde. Generally, B97D and MO62X calculations gave similar results, while barriers computed at B3LYP 5 – 15 kcal/mol higher due to pronouncedly high contribution of association enthalpies. The latter is due to neglect of repulsions at short distances.

The lowest barrier for the attack of DMSM was calculated for ketone **1** with the most remoted reactive center from the cage (14.3 and 14.2 kcal mol, respectively at B97D and MO62X). For the analogous respective diamantane ketone **4** the relative positions of the reactive centers and critical O=C•••CH$_2$=S and C-H•••H-C bond

distances are similar. Thus, the influence of the distant cage moiety within 3 C-C bonds is minimal. As a result, the barriers calculated for the attack of the DMSM on ketones **1** and **4** (14.6 (14.3) and 15.8 (14.2) kcal/mol respectively at B97D and MO62X) are similar, and in accord with the experimental rate constants (k=274•10^{-5} L^2/(mol^2*s) for ketone 4, k=174•10^{-5} L^2/(mol^2*s) for ketone 1).
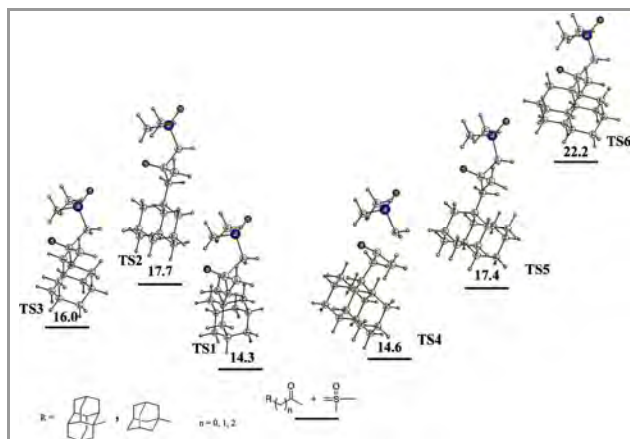
*Scheme.2 Relative barriers for the attack of DMSM on **1-6**. Relative ΔG_{298} at B97D/6-31+G(d,p), PCM, DMSO in kcal mol^{-1}, critical bond distances in Å..*

For the most bulky ketones **3** and **6** the barriers of the methylenation reaction are much higher than that for ketones **1** and **4**. The highest computed barrier for the attack of DMSM on the carbonyl group was calculated for ketone **6** (22.2, 23.4 and 34.1 kcal/mol, respectively at B97D, MO62X, and B3LYP).

Conclusions

Counterintuitive one can't predict reactivity of the diamondoidyl ketones/derivatives by distance between cage and carbonyl/reactive center. We assumed, that adamantane fragment causes larger steric hindrance, then diamantane. While on the short distances, diamantane scaffold possesses pronouncedly higher steric bulkiness, than adamantane scaffold. Topological difference bet-ween the positional isomers is crucial. Diamantane substituted in the 4-position, causes the same steric hindrance/effect as adamantane; rate constants for 1-adamantylmethyl ketone and 4-diamantylmethyl ketone are similar. While 1-diamantyl substituent has pronoun-cedly larger steric hindrance, then adamantyl, and hamper the reaction on the short distances. Thus 1-diamantyl-methylketone is inert towards DMSM, while 4-derivatives is quite reactive (k=4.86 •10^{-5} L^2/(mol^2*s)). Further investigations should take this into account.

References

[1] Schwertfeger H. Diamonds are a Chemist's Best Friend: Diamondoid Chemistry Beyond Adamantane / Schwertfeger, H., Fokin, A. and Schreiner, P // Angewandte Chemie International Edition – 2008 – 47, p 1022–1036.