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STRUCTURE–REACTIVITY RELATIONSHIP IN DIELS–ALDER REACTIONS OBTAINED USING THE CONDENSED REACTION GRAPH APPROACH

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By the structural representation of a chemical reaction in the form of a condensed graph a model allowing the prediction of rate constants (log*k*) of Diels–Alder reactions performed in different solvents and at different temperatures is constructed for the first time. The model demonstrates good agreement between the predicted and experimental log*k* values: the mean squared error is less than 0.75 log units. Erroneous predictions correspond to reactions in which reagents contain rarely occurring structural fragments. The model is available for users at https://cimm.kpfu.ru/predictor/.

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INTRODUCTION

Cycloaddition is one of the most used and important reactions in synthetic chemistry. They are especially interesting because these reactions lead to the formation of aromatic and unsaturated rings, which is important for medical chemistry [1]. Recently increased interest in them is explained by that many click chemistry reactions [2], especially those used in bioorthogonal chemistry [3], are cycloaddition reactions, e.g., azide–alkyne [4], alkyne–nitron [5], tetrazine–alkene [6], and so on. Perspectives to use a cycloaddition reaction in bioorthogonal chemistry are, as a rule, determined by its rate with regard to very low concentrations of reagents needed to provide biocompatibility [7]. Moreover, taking into account the possible formation of regioisomers in the cycloaddition reaction, their ratio can be estimated knowing the reaction rate constants. Thus, it is extremely important to predict cycloaddition reaction rates. In general, the reaction rate constants enable the estimation of not only the dynamics of chemical processes but also the calculation of product yields and their ratio.

Still, there are no well-established approaches for the reliable estimation of cycloaddition reaction rates in a wide range of solvents. The application of quantum chemistry methods for predicting the rates and conditions of cycloaddition reactions is not efficient because of difficulties to handle solvent effects and the conformational flexibility of molecules, as well as due to high computational costs. Methods based on the use of simple correlations, substituent and solvent constants are more successful in predicting rate constants [8, 9]. However, they can be applied only to relatively small congeneric data

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