k_i is a coefficient reflecting the springs stiffness.

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Impact of substituents on thermal recyclization of 2-iminocoumarins: experimental, computational and theoretical insights

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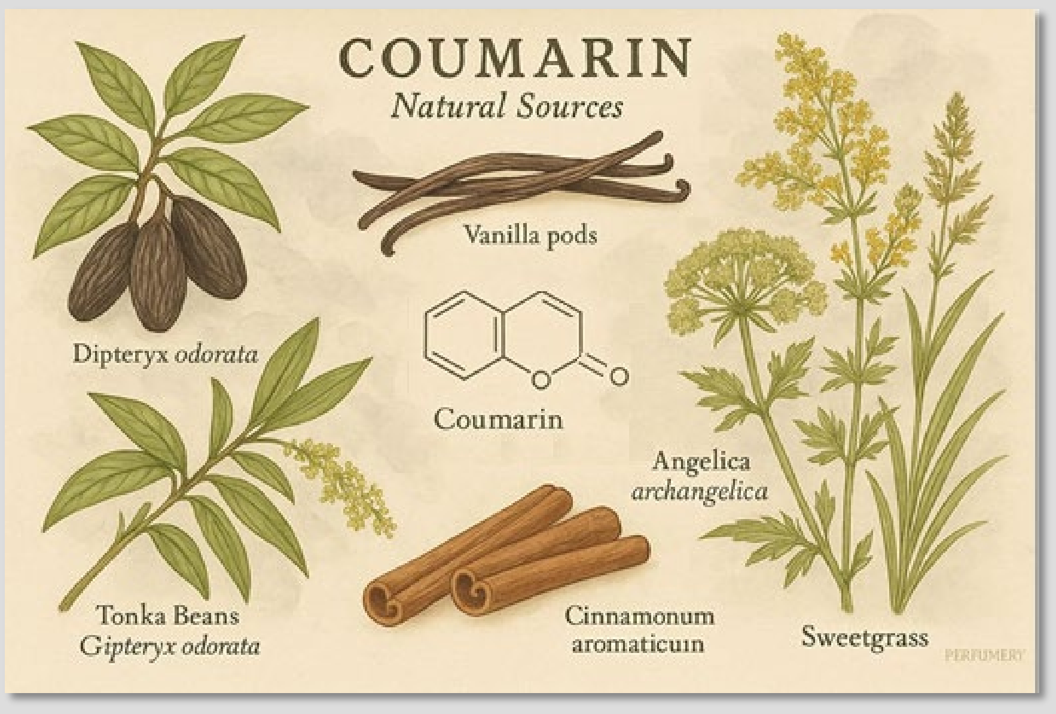
Background

- Coumarin derivatives have garnered a significant interest and found diverse applications last decades. Particularly, they are considered as effective medicines possessing antimicrobial, antituberculosis and antioxidant activity, and anti-Alzheimer's agents.
- A unique and efficient pathway of obtaining these compounds is recyclization reaction occurring *via* heating up to a certain temperature which can be properly registered by means of thermogravimetry analysis (TGA).
- The recyclization temperature were reported to be influenced significantly by substituents. Meanwhile, there is a clear lack of systematic study of this issue.



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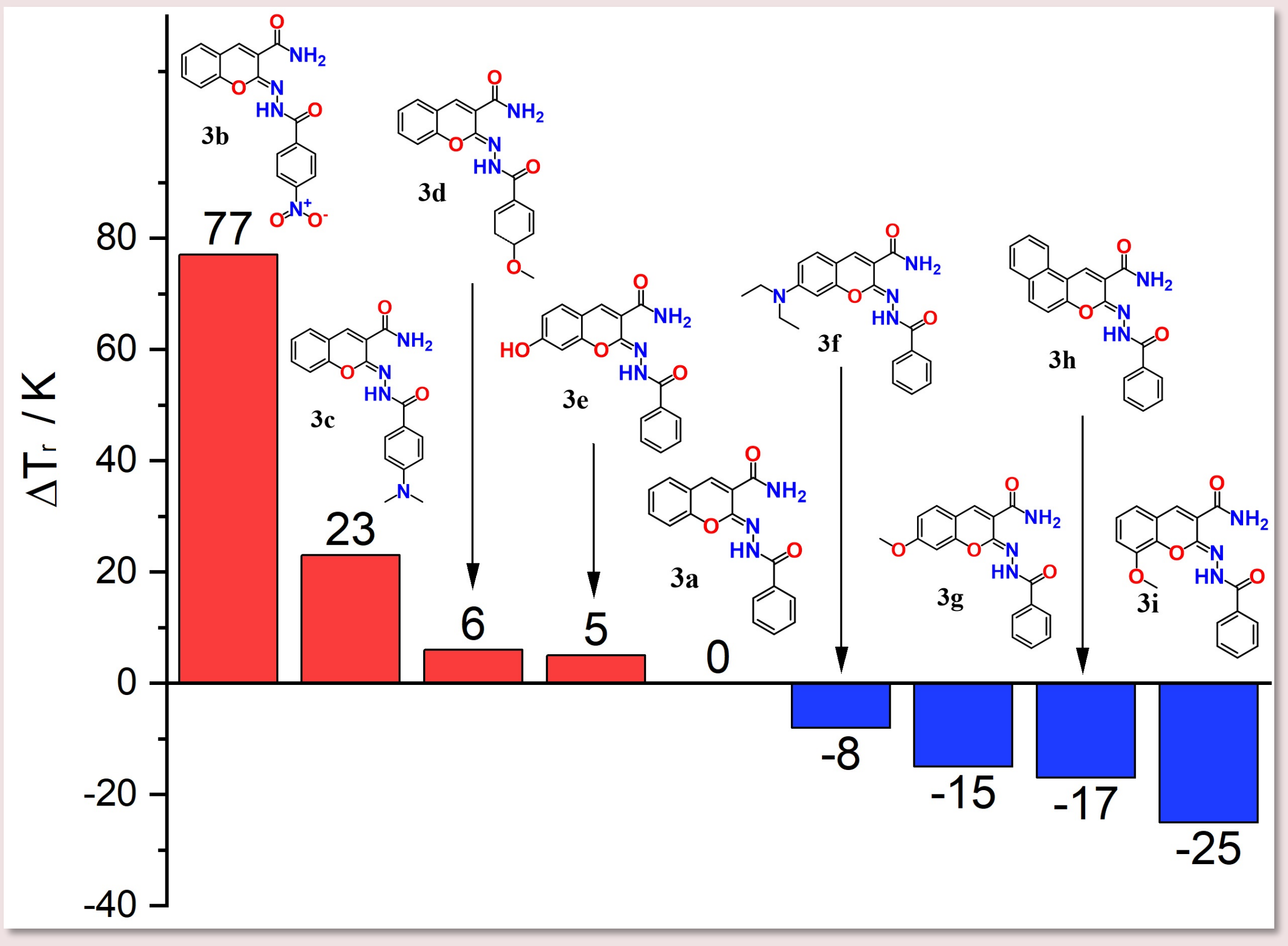
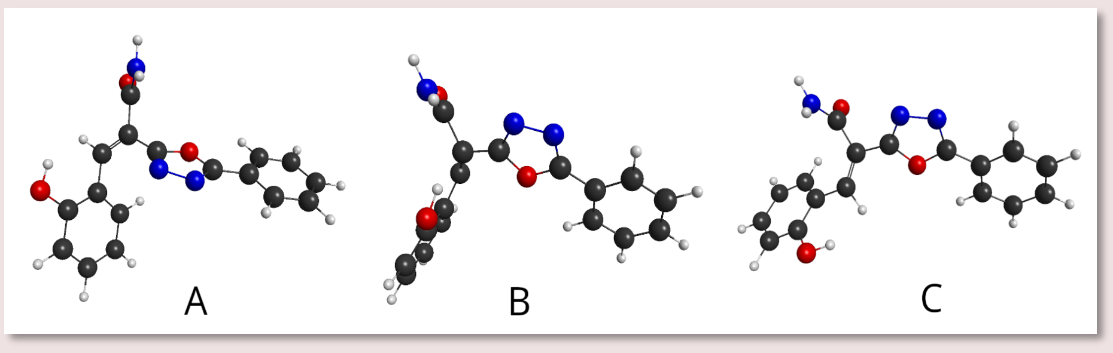
Experimental

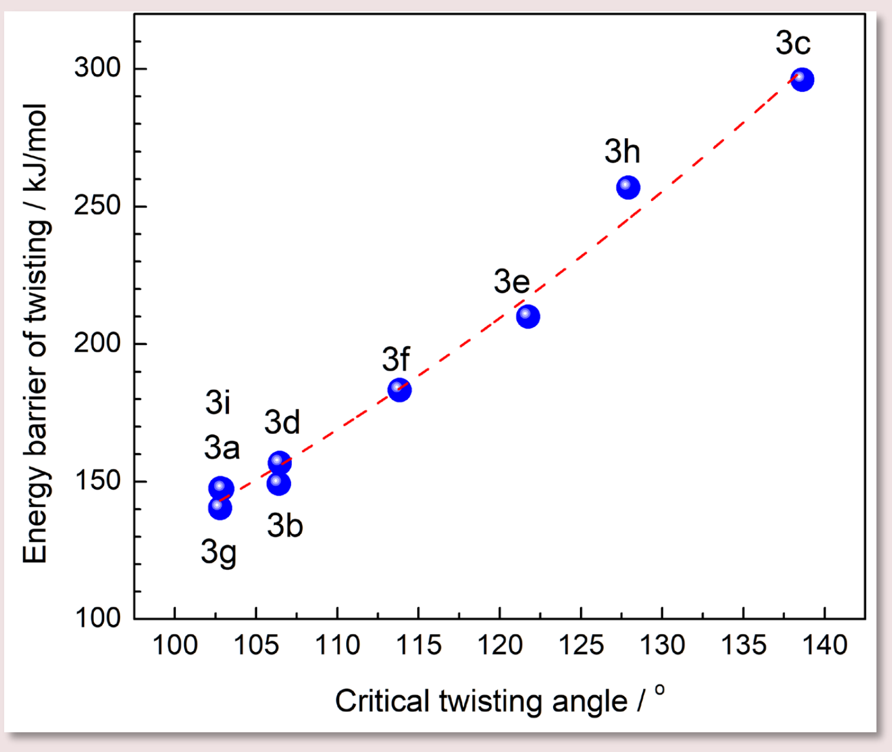


- A set of 2-(2-benzoylhydrazineylidene)-2H-chromene-3-carboxamide derivatives (**2-iminocoumarins**) was synthesized, differed both in electrophilicity and position of the substituents, which formed 3-(1,3,4-oxadiazol-2-yl)-coumarin derivatives by the recyclization reaction
- It was established that exploiting n-BuOH as a solvent for the recyclization is optimal due to the best results in yield and purity with reasonable full conversion time, relatively high operational temperature as well as correspondence to the principles of green chemistry
- TGA data revealed a significant shift of the recyclization temperature (ΔT_r) depending on the substituent nature.
- The values of ΔT_r ranged within *ca.* 100 K and were both positive and negative relative to the unsubstituted compound **3a**
- Activation energy of recyclization was determined for the unsubstituted compound by means of TGA

Calculations

Representative optimized geometries of the intermediate compounds formed during E-Z isomerization (the 3rd stage of the recyclization reaction)

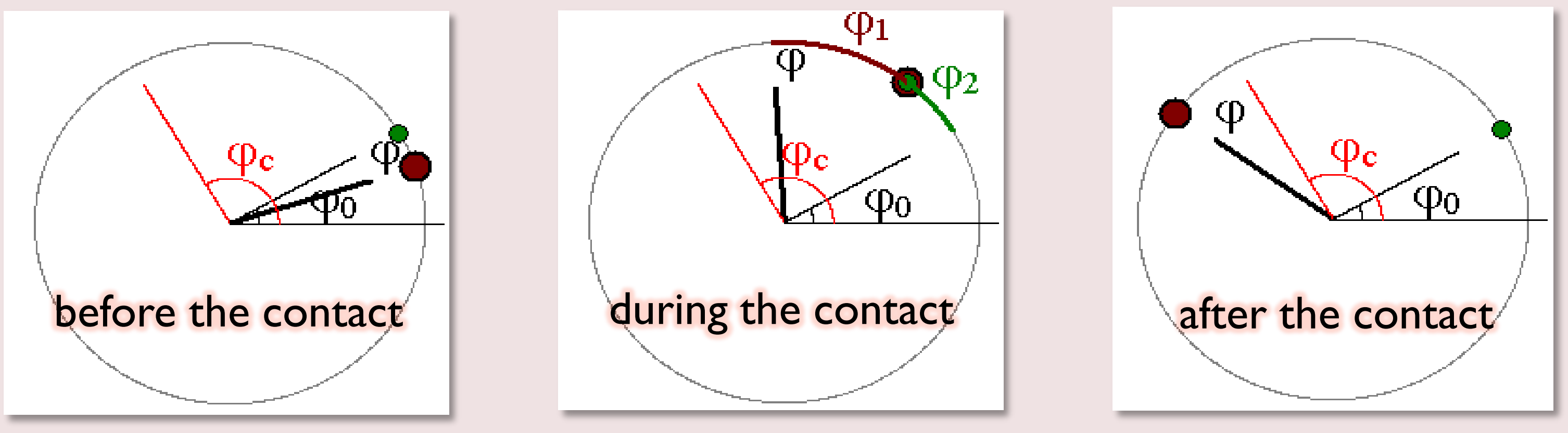




Parabolical relation was found between the energy barrier of intramolecular twisting during E-Z isomerization and the critical twisting angle. Based on this finding, occurring some steric hindrances, which arise during intramolecular rotation and contribute into the twisting energy, was hypothesized

- Quantum-chemical calculations at 6-31G (d) level of theory using PM3(d,p) were applicated to explore selected stages of the reaction, namely intramolecular rotation
- Significant changes in the energy barrier of intramolecular twisting as well as changes in polarity of the double bonds involved in the reaction was shown, which is obviously related to substituents' electrophilicity and position

Theory



Hindered intramolecular rotation

$$E = \frac{1}{2}\frac{k_2 k_1}{k_1 + k_2}(\varphi - \varphi_0)^2$$

Critical parameters
(i – different compounds)

$$E_c^i = \frac{1}{2}\frac{k_2 k_1}{k_1 + k_2}(\varphi_c^i - \varphi_0)^2$$

E is the deformation energy
E_c is the energy barrier of twisting
φ is the current angle of intramolecular rotation
φ_0 is the angle when the contact arises between the rotating molecular moieties (hooking)
φ_c is the critical twisting angle (the angle of unhooking)
φ_1 , φ_2 are the angles of elastic deformation of each moiety (twisting angles)
k_1, k_2 are elastic coefficients (stiffness) of the moieties

- The developed mathematical model based on linear elastic theory supposed that some moieties of the coumarin derivatives could contact each other during intramolecular rotation resulting to certain elastic deformations
- The model has analytically justified the shape of the relation between the rotation angle and the energetic cost of rotation, which was obtained by means of the calculations

Conclusions

- Significant shift in the recyclization temperature of the synthetized 2-iminocoumarins was shown by means of a thermoanalytical technique. For various substituents, the shift ranged within 100 K and was both positive and negative relative to the unsubstituted compound.
- Quantum-chemical calculations have revealed significant changes in the energy barrier of intramolecular twisting as well as in the polarity of the double bonds involved in the reaction depending on substituents' nature and position.
- Occurring some additional relevant factors, namely, steric hindrances, which arise during intramolecular rotation and contribute into the twisting energy, was hypothesized grounding on the calculation results. These hindrances can originate from direct contact between certain molecular moieties during rotation and cause their elastic deformation.
- The model based on linear elastic theory was developed. It has analytically justified the shape of the relation between the critical twisting angle and the energy barrier of twisting, which was obtained by means of the calculations. Actually, it strictly confirms indirect impact of substituents on intramolecular events occurring distantly from their localization.
- Generally, such combined experimental, quantum-chemical and theoretical insight appeared to be fruitful for exploring the substituents' impact and may see increased application in the future.