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National Recovery and Resilience Plan
OF THE REPUBLIC OF BULGARIA

Reactivity in Friedel-Crafts Aromatic Benzylation
The Role of the Electrophilic Reactant

Computational Chemistry Synthesis & Spectroscopy

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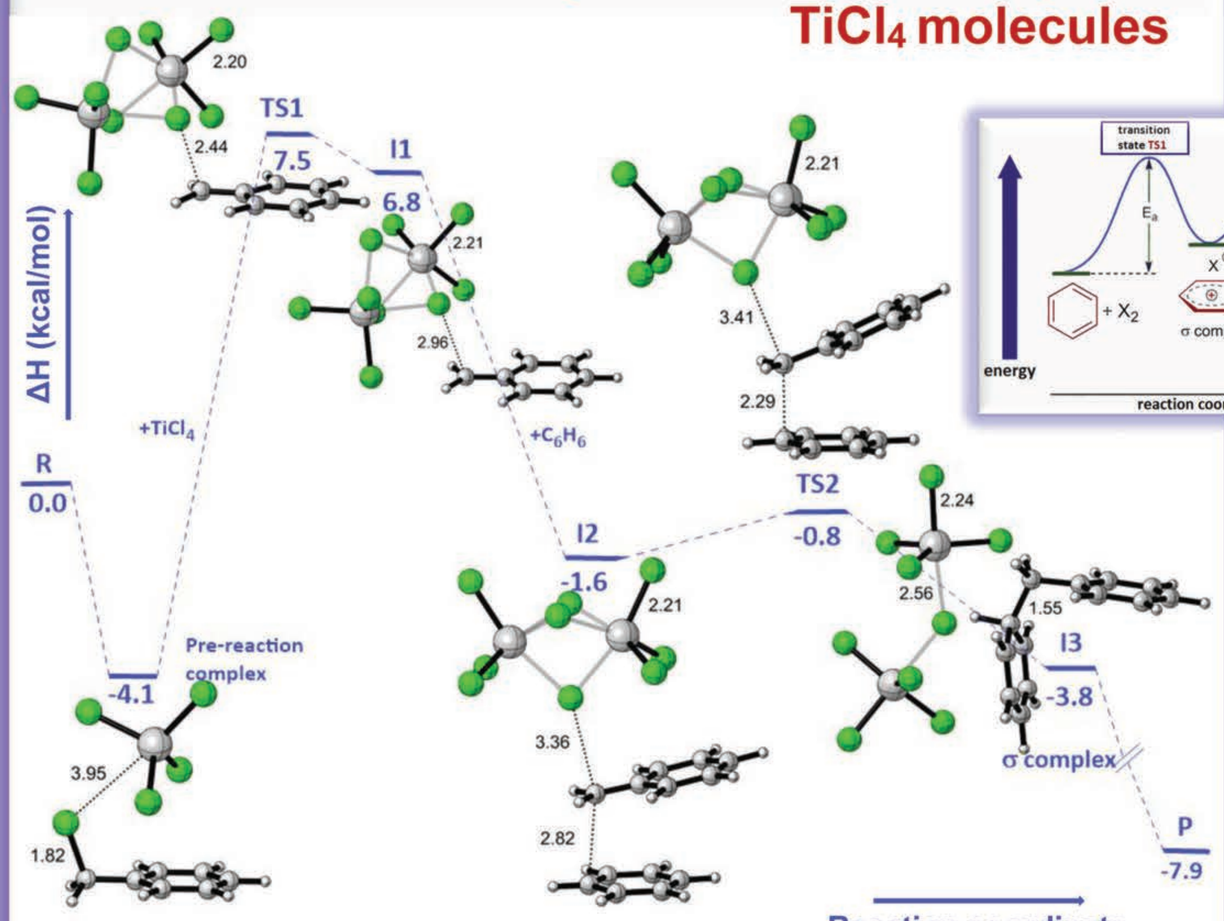
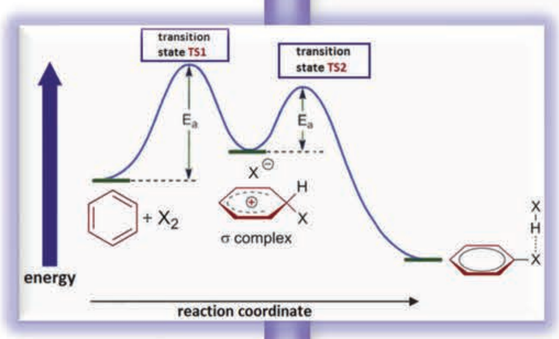
DFT calculations are used to study the $TiCl_4$–catalyzed Friedel–Crafts benzylation of benzene with substituted benzyl chlorides in nitromethane. The reaction is unusual for electrophilic aromatic substitution, showing no kinetic dependence on the aromatic substrate. M06-2X computations with several basis sets and solvent models revealed four intermediates and confirmed that combining computed enthalpy barriers with experimental entropy data best reproduces the observed rate behavior. Reactivity trends among ten ring-substituted benzyl chlorides correlate with the C–Cl bond dissociation energy and the Hirshfeld charge at the chlorine in substituted benzyl chlorides.

Computational methods

- The computational results were conducted using the M06-2X density functional combined with the 6-311+G(d,p) basis set.
- The 6-311+G(2df,2p) and def2-TZVPP basis sets were used to assess the influence of the basis set.
- To estimate the influence of the dispersion effects on the reaction barriers calculations are performed with M06-2X(D3)/6-311+G(d,p)
- SMD and CPCM were the used models to describe the effects of the solvent.
- IRC method was used in connecting the critical structures along the reaction path.

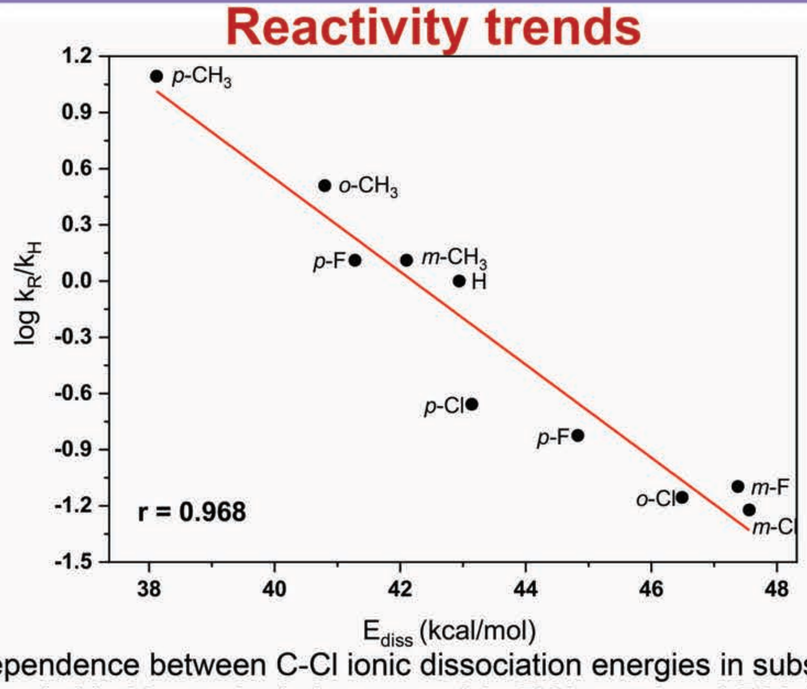
Mechanism of benzylation, catalyzed by two $TiCl_4$ molecules



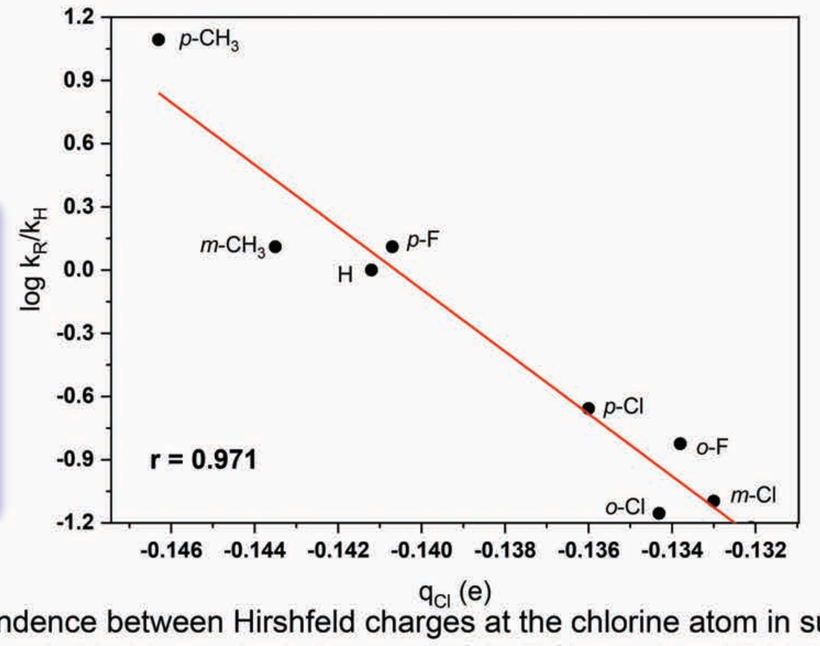


Structure	ΔH (kcal/mol)	ΔG_{est} (kcal/mol)	ΔG_{exp} (kcal/mol)
R	0.0	0.0	
Pre-reaction complex	-4.5	–	
TS1	7.5	13.1	18.3
I2	-1.6	–	
TS2	-0.8	(4.8)	
I3 σ-complex	-3.8	–	
P	-7.9	–	

Reactivity trends



Dependence between C-Cl ionic dissociation energies in substituted benzyl chlorides and relative rates of the$TiCl_4$-catalyzed Fridel-Crafts benzylation of benzene in nitromethane solvent



Dependence between Hirshfeld charges at the chlorine atom in substituted benzyl chlorides and relative rates of the$TiCl_4$-catalyzed Fridel-Crafts benzylation of benzene in nitromethane solvent

Conclusions

- Geometry optimization and vibrational analysis were performed for all studied structures.
- The critical structures along the reaction pathway were characterized. The rate-determining step was identified.
- The order of the kinetic equation of the reaction and the absence of arene participation in it were confirmed.
- Two possible mechanisms of Friedel–Crafts benzylation catalyzed by $TiCl_4$ were investigated. It was found that the mechanism catalyzed by two $TiCl_4$ molecules is energetically more favorable.
- Factors affecting reactivity were determined – the dissociation energy of the C–Cl bond and the charge on the chlorine atom in substituted benzyl chlorides.

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