Role of substituents in Hofmann-Löffler-Freytag synthesis of nicotine. A quantum chemical study

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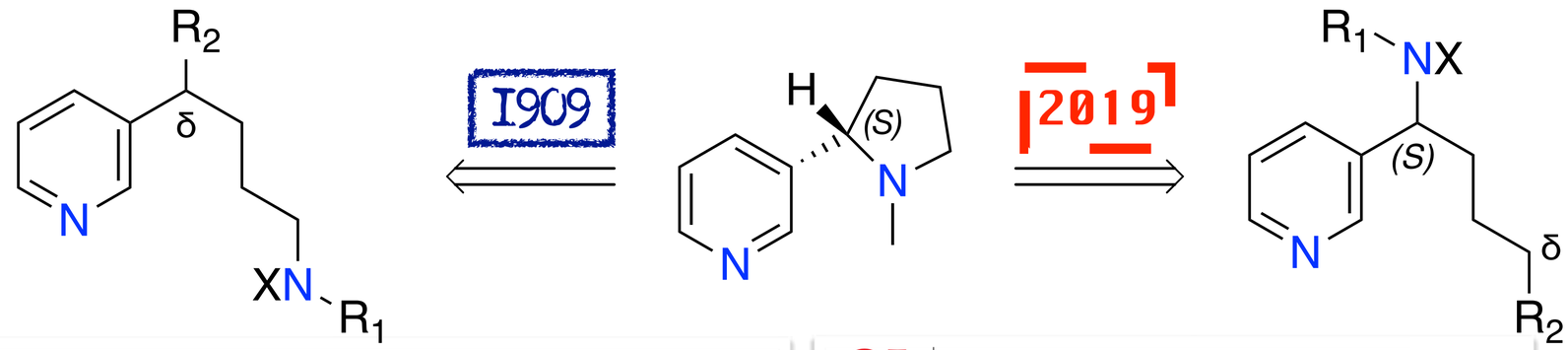
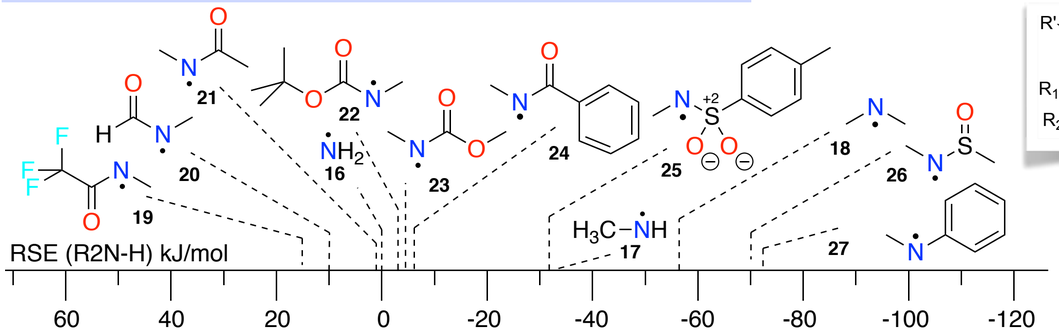
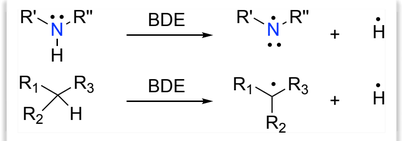
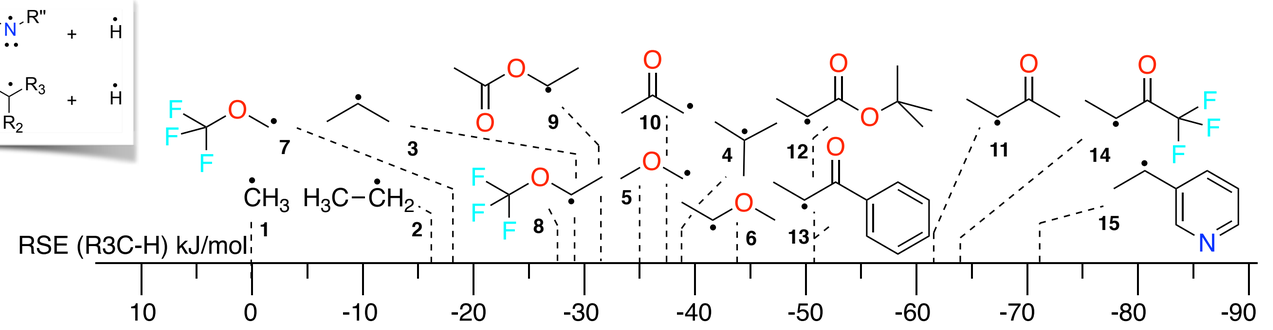
Recently, synthesis of (*S*)-nicotine has been achieved by using Hofmann-Löffler-Freytag (HLF) methodology. The original procedure using the same methodology has been done at the beginning of the 20th century, but the products were a racemic mixture. Crucial step in the HLF reaction pathway is hydrogen atom transfer (HAT) from the *N*-centered radical to *C*-centered radical. Del Castillo and Muniz have achieved retention of stereoconfiguration by using a protective group on nitrogen and an additional activation of primary C atom via O-methylation.

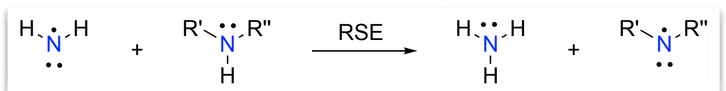


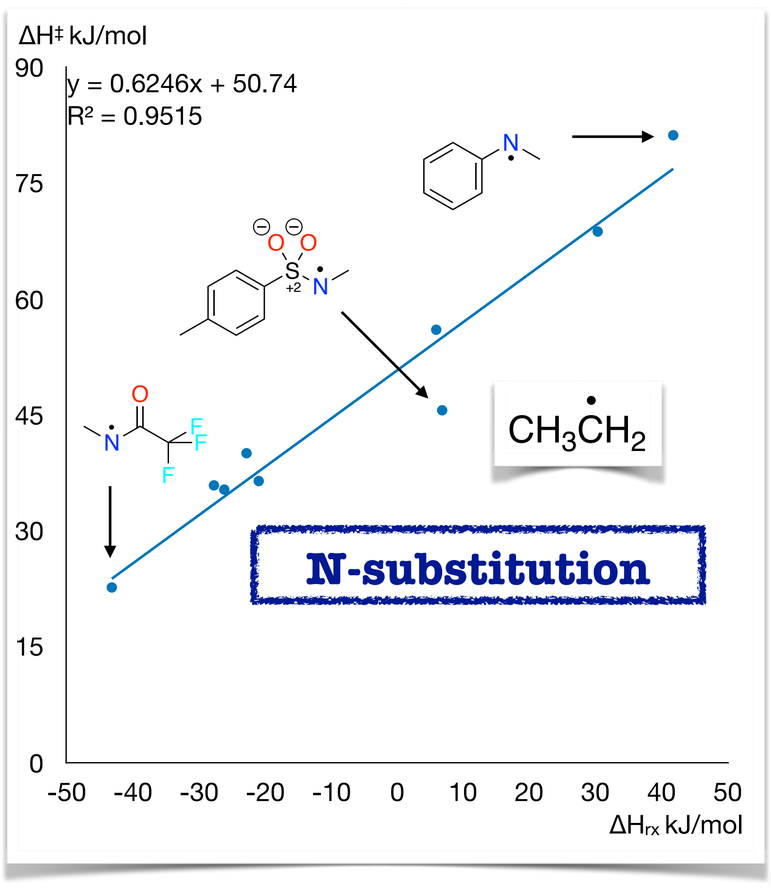






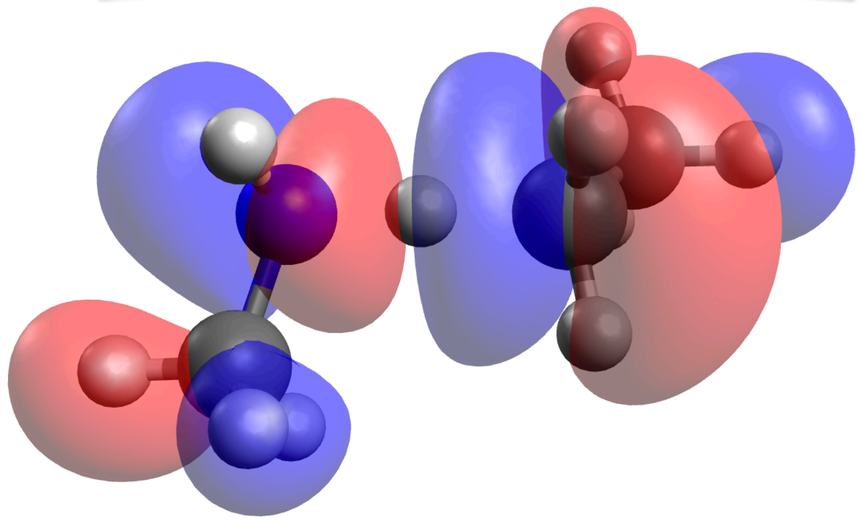
Relative stabilization energies of *N*-centered radicals





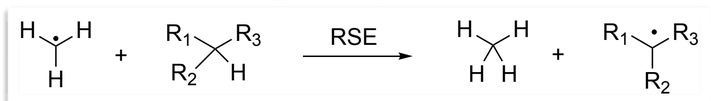
Intermolecular HAT-reactions

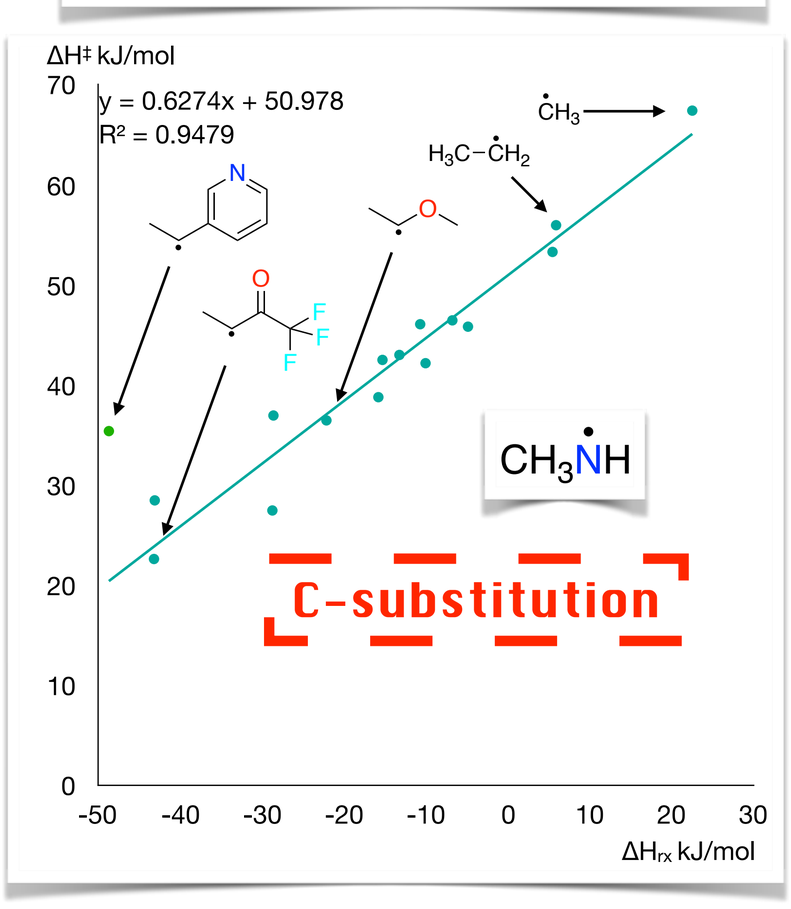
In order to find better synthetic routes for the original (racemic mixture) product and the stereoselective one, both *N*- and *C*-substitution effects on the HAT step of the reaction were quantified.



SOMO TS orbital
A characteristic of hydrogen atom transfer (HAT) processes.
Node is located at transferring hydrogen atom.

Relative stabilization energies of *C*-centered radicals

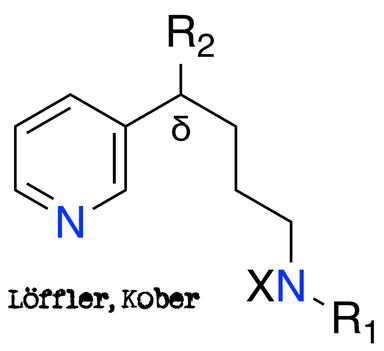




- hydrogen atom transfer (HAT) VS proton coupled electron transfer (PCET) elucidated via SOMO orbital- HAT wins
- relationship between ΔH_{rx} and $\Delta H^{‡}$ of the intermolecular HAT reactions is linear complying to Bell–Evans–Polanyi (BEP) principle
- for spontaneous reaction:
  - destabilisation effect on *N*-centred radicals
  - stabilisation effect on *C*-centred radicals
- amide-type *N*-centered radicals are most destabilised making reaction with primary C-atom feasible
- often used tosyl protecting group is mediocre
- same functional group has stabilising effect on *C*-centred radical and destabilising effect on *N*-centred radical

- intramolecular HAT reactions for stereoselective and non-stereoselective synthesis of (*S*)-nicotine
- precursor evaluation as pre-optimisation of synthesis-finding the thermodynamically and kinetically favourable route of nicotine synthesis.
- BEP principle works here (similar intercept and slope)
- effect of N-substituents on HAT step of the non-stereoselective synthesis observed in 75 kJ/mol range
- very stable pyridyl *C*-centered radical is formed
- effect of N- and C- substituents on the stereoselective synthesis observed over 50 kJ/mol range
- synergistic effect of the substituents evaluated across 80 kJ/mol range.

Intramolecular HAT-reactions



	R1	R2	ΔH_{rx} kJ/mol	$\Delta H^{‡}$ kJ/mol
L1	-H	-H	-47.85	45.65
L2	$-CH_3$	-H	-23.37	54.20
L3	-Tos	-H	-43.00	30.95
L4	-*t*-Boc	-H	-84.50	20.90
L5	$-COCH_3$	-H	-87.22	16.19
L6	$-COCF_3$	-H	-99.30	4.76
			a	0.58
			b	66.14
			R^2	0.94

- GaussView & Gaussian 16
- Geometry optimisation, frequency and IRC calculations @B3LYP/6-31G(d)
- conformation analysis: PCMODEL 10 software
- Single point energies @ROB2-PLYP/G3Large & @G3B3
- Cluster Isabella @SRCE

	R1	R2	ΔH_{rx} kJ/mol	$\Delta H^{‡}$ kJ/mol
M1	-H	-H	4.04	59.77
M2	$-CH_3$	-H	29.07	71.28
M3	$-CH_3$	$(-C_\gamma OC_\delta H_2)$-H	5.29	72.51
M4	$-CH_3$	$-OCH_3$	-8.10	45.25
M5	$-CH_3$	$-COCH_3$	-11.22	50.13
M6	$-CH_3$	$-COCF_3$	-21.35	37.91
		a		0.71
		b		56.41
		R^2		0.88

	R1	R2	ΔH_{rx} kJ/mol	$\Delta H^{‡}$ kJ/mol
M1	-H	-H	4.04	59.77
M11	-Tos	$-OCH_3$	-34.28	37.88
M12	$-COCH_3$	$(-C_\gamma OC_\delta H_2)$-H	-41.19	53.85
M13	$-COCH_3$	$-COCH_3$	-66.28	30.49
M14	$-COCF_3$	$-COCF_3$	-74.86	34.05
		a		0.35
		b		58.01
		R^2		0.84

	R1	R2	ΔH_{rx} kJ/mol	$\Delta H^{‡}$ kJ/mol
M1	-H	-H	4.04	59.77
M7	-Tos	-H	-2.48	46.37
M8	-*t*-Boc	-H	-26.40	37.83
M9	$-COCH_3$	-H	-27.56	33.55
M10	$-COCF_3$	-H	-43.69	21.58
		a		0.70
		b		53.37
		R^2		0.97

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- best non-stereoselective synthesis is **L6**
- spontaneous stereoselective synthesis C-substiution:
- **M5** and **M6**
- spontaneous stereoselective synthesis N-substiution: **M8**, **M9** and **M10**
- better combinations of N- and C-substituents **M13** & **M14**
- quantum chemical calculations should be used in planning phase of experiments to pre-optimize synthesis

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