

Computational studies and reactivity of nucleophiles in benzylation reactions

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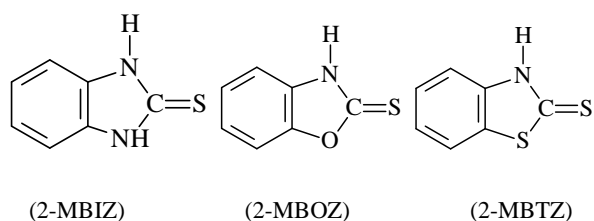
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The nucleophilic substitution reactions of benzyl bromide using 2-mercapto benzimidazole, 2-mercaptobenzoxazole and 2-mercaptobenzothiazole as nucleophiles have been studied in methanol and acetone media. The higher reactivity of 2-mercaptobenzimidazole is attributed to the presence of two nitrogen atoms holding a pair of electrons on either side of the >C=S group. The heat of formation, ΔH_f , computed from AM1 studies indicates that the reactivity of the nucleophiles is related to ΔH_f , and HOMO-LUMO gap of the nucleophile.

Heterocyclic compounds are a biologically important class of compounds. Though vast information on synthetically important benzylation of different bases is available in the literature¹⁻⁶, information on benzylation of heterocyclic ring systems appears to be scanty except for a few reports from our laboratory⁷⁻¹¹. We report herein, results on the kinetic study of benzylation of 2-mercaptobenzimidazole (2-MBIZ), 2-mercaptobenzoxazole (2-MBOZ) and 2-mercaptobenzothiazole (2-MBTZ) using benzylbromide as substrate in methanol and acetone media.



Quantum chemistry has provided powerful tools to calculate theoretically electron densities at different atoms in a molecule, heats of formation (ΔH_f) dipole moments (μ), energies of frontier orbitals, all of which help us in predicting the reactivities and reaction paths of different compounds. Rastogi and co-workers¹² applied the AM1 method to study the decomposition reaction path of formamidine. De and

co-workers¹¹ have carried out quantum mechanical study of gas phase reactions of H₂S with Cl₂ and SO₂. They have also studied the reaction of sulphur monochloride with Cl₂ by applying the AM1 method with complete geometry optimization. Rajeswara Rao¹⁴ performed AM1 study on conformations of α -methyl dopa. In the present note, results of AM1 studies in the reactions of 2-MBIZ, 2-MBOZ and 2-MBTZ with benzylbromide is reported. An attempt is also made to correlate the reactivities of these nucleophiles with ΔH_f and HOMO-LUMO gaps.

Experimental

Benzylbromide (Riedel), 2-mercaptobenzimidazole (Aldrich), 2-mercaptobenzoxazole (Aldrich), 2-mercaptobenzothiazole (Aldrich) were used without further purification. AR grade methanol and acetone were purified by literature methods¹⁵. The progress of the reaction was followed by studying the conductance of the reaction mixture at different time intervals. Preliminary study indicated that the reaction was first order with respect to [BzBr] and [nucleophile] in each case. The second order rate constants, k_{II} , have been computed using the relationship¹⁶:

$$k_{II} = \frac{1}{at} \frac{C_t - C_0}{C_\infty - C_t}$$

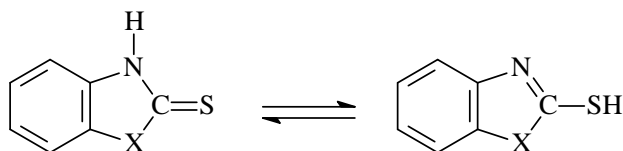
where 'a' is initial concentration of the reactants C_t is the conductance of the reaction mixture at time t , C_0 and C_∞ are respectively the conductance of the reaction mixture at the beginning and after completion of the reaction. A plot of $\frac{C_t - C_0}{C_\infty - C_t}$ against time is

linear in each case. The k_{II} value is computed from the slope of this plot. Duplicate runs gave k_{II} values within $\pm 5\%$ error. The product in each case was the corresponding S-benzyl derivative, which was identified by recording their IR spectra. In each case the spectra indicated the thioether link ($\approx 700 \text{ cm}^{-1}$) and S-CH₂ group ($\approx 2700 \text{ cm}^{-1}$ and $\approx 1400 \text{ cm}^{-1}$)(ref. 17).

In the view of the identified product and first order nature of the reaction with respect to substrate and the

nucleophile in each case, the reaction scheme may be represented as shown in Scheme 1.

The nucleophiles used in this study can exist either in thione or in mercapto form.

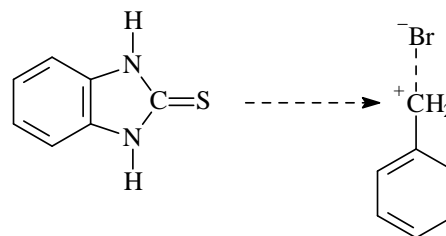


Results and discussion

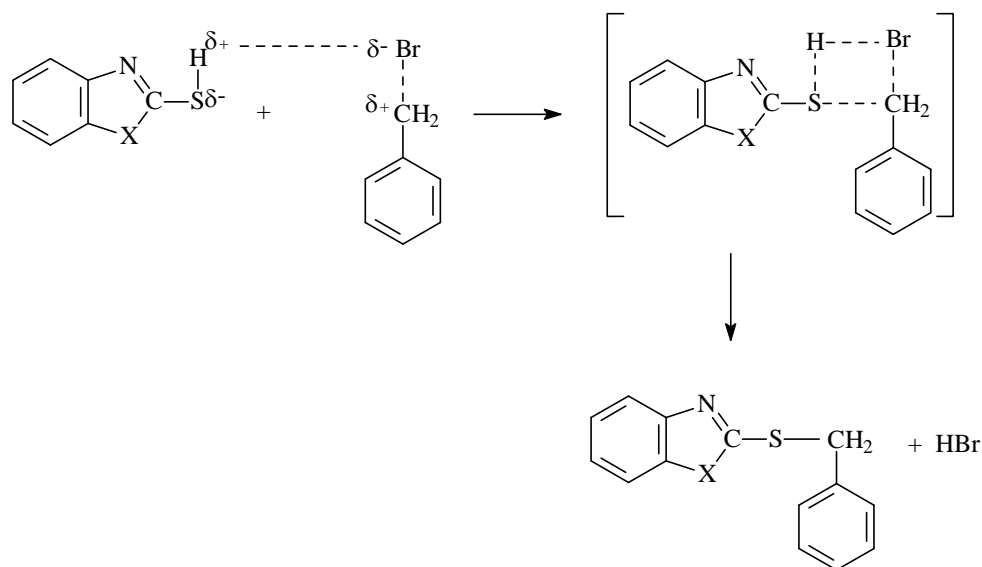
The second order rate constants, determined in 100% methanol and 100% acetone, using 0.02 mol dm^{-3} benzylbromide and 0.02 mol dm^{-3} nucleophile in the temperature range 293-313 K are given in Table 1. A glance at the rate constants presented in Table 1 indicates that the order of reactivities of these three structurally similar nucleophiles is: 2-MBIZ > 2-MBTZ >> 2-MBOZ in methanol as well as in acetone.

In both the media, 2-MBIZ reacts faster as compared to 2-MBTZ and 2-MBOZ.

The highest reactivity of 2-MBIZ among the three nucleophiles is due to the presence of two nitrogen atoms holding a pair of electrons on either side of $>\text{C}=\text{S}$,



which increases the electron donating capacity of 'S' to form a bond with benzylic carbon atom. In 2-MBTZ and 2-MBOZ, one nitrogen atom and either 'S' or 'O' atoms are present adjacent to $>\text{C}=\text{S}$ and



X=NH, S, O for 2-MBIZ, 2-MBTZ and 2-MBOZ respectively.

Scheme 1

Table 1—Rate constants at different temperatures and thermodynamic parameters in the reactions of benzylbromide with different nucleophiles. { * T = 303 K, [Benzylbromide] = [Nucleophile] = $0.02 \times 10^{-2} \text{ mol dm}^{-3}$ }

Solvent	Nucleophile	$k_{II} \times 10^4 \text{ (dm}^3 \text{ mol}^{-1} \text{ s}^{-1})$ at temp. (K)				E_a (kJ mol ⁻¹)	$^*\Delta H^\ddagger$ (kJmol ⁻¹)	$^*\Delta S^\ddagger$ (JK ⁻¹ mol ⁻¹)	$^*\Delta G^\ddagger$ (kJmol ⁻¹)
		293	298	303	313				
Methanol	2-MBIZ	85.02	158.91	401.26	732.61	43.02	40.52	-146	84.76
	2-MBTZ	12.61	22.40	37.24	123.02	120.51	118.01	-105	86.24
	2-MBOZ	4.50	7.02	10.62	40.00	68.93	66.41	-83	91.51
Acetone	2-MBIZ	70.84	111.09	172.92	--	74.58	72.08	-41	84.50
	2-MBTZ	30.33	78.78	115.05	--	95.11	92.61	-23	85.53
	2-MBOZ	3.40	4.47	6.35	--	47.87	45.85	-150	90.69

Table 2—Results of AM1 calculations in the reactions of benzylbromide with different nucleophiles

Comp.	ΔH_f (kJ mol ⁻¹)	$E(\text{HOMO})$ (eV)	$E(\text{LUMO})$ (eV)	ΔE (eV)
2-MBIZ (Thioneform)	274.76	-8.430	-0.477	7.953
2-MBIZ (Mercaptoform)	290.03	-8.516	-0.125	8.391
2-MBTZ (Thioneform)	224.48	-8.694	-0.664	8.030
2-MBTZ (Mercaptoform)	226.56	-8.447	-0.847	7.600
2-MBOZ (Thioneform)	146.27	-8.899	-0.670	8.229
2-MBOZ (Mercaptoform)	159.05	-8.829	-0.474	8.355
Benzyl bromide	80.05	-9.610	-0.050	9.560
HBr	-43.92	-11.464	1.158	12.622
S-Benzyl 2-MBIZ	378.72	-8.278	-0.219	8.059
S-Benzyl 2-MBTZ	312.65	-8.366	-0.533	7.833
S-Benzyl 2-MBOZ	245.63	-8.535	-0.399	8.136

hence the rate decreases. In 2-MBOZ, the more electronegative oxygen atom pulls electrons towards itself and hence, the electron availability on 'S' for bond formation with the benzylic carbon atom will decrease. Therefore, lowest rate is observed. In 2-MBTZ which contains less electronegative sulphur atom (compared to oxygen) adjacent to >C=S, the electron donation is relatively easier. Hence, as compared to 2-MBOZ, a higher rate is observed.

Semiempirical molecular orbital calculations were performed on the molecules used in the present system using AM1 method¹⁸ included in MOPAC-93. Geometry calculations in the ground state were completely optimized (keyword PRECISE, equivalent to GNORM = 1.0) until the lowest energy conformation was reached. The initial molecular geometry was adopted as Pople's standard data¹⁹. Heat of formation, the energies of frontier orbitals, E_{HOMO} and E_{LUMO} of the reactants and products calculated are given in Table 2.

The energies of HOMOs of all the nucleophiles are higher than that of the substrate, benzylbromide. This is an indication that the electrons of the nucleophiles can be easily attracted by the approaching electrophile. According to perturbation theory, the HOMO of the nucleophile interacts with the HOMO of the substrate forming bonding orbitals of the product²⁰. This energy transfer during the formation of the products HBr and the corresponding S-benzyl derivative from the reactants are 1.18 eV, 0.916 eV and 0.711 eV with 2-MBIZ, 2-MBTZ and 2-MBOZ

Table 3—The computed electron densities on 'S' atom of 2-MBIZ, 2-MBTZ and 2-MBOZ

Nucleophile	>C = S group	>C – SH group
2-MBIZ	6.2230	5.8169
2-MBTZ	6.0943	5.7872
2-MBOZ	6.0847	5.7274

respectively. Due to HOMO-HOMO interactions of the nucleophile and benzyl bromide, the energy is liberated in the formation of HBr and absorbed in the formation of the second product, S-benzyl derivative. This energy transfer during the reaction is in the order: 2-MBIZ > 2-MBTZ > 2-MBOZ, which is also the observed order of reactivity. The heats of formation of these nucleophiles ΔH_f are also in the order: 2-MBIZ > 2-MBTZ > 2-MBOZ. According to Fleming²¹ and Pearson²² the ability of a nucleophile to donate electrons to electrophiles to begin the process of bond formation can be correlated with the HOMO-LUMO gap of the nucleophile. The reactants with smaller HOMO-LUMO gaps tend to be more reactive than those with larger gaps. In the present study, these HOMO-LUMO gaps (Table 2) are 7.953, 8.030 and 8.229 eV with 2-MBIZ, 2-MBTZ and 2-MBOZ respectively. Thus, the higher reactivity of 2-MBIZ observed is attributed to smaller HOMO-LUMO gap compared to that of the other two nucleophiles. These gaps are in the order 2-MBIZ < 2-MBTZ < 2-MBOZ, which is in consonance with the observed order of reactivity. The computed electron densities on 'S' atom of the thione and mercapto groups of the nucleophiles are presented in Table 3. These values are in the order: 2-MBIZ > 2-MBTZ > 2-MBOZ, which is also the order of reactivity of these nucleophiles in both methanol and acetone media. Thus, it can be concluded that the observed order of reactivities among the three nucleophiles studied is related to their heats of formation, HOMO-HOMO interaction energy of the two reactants, HOMO-LUMO gaps of the nucleophiles, and the electron densities on the sulphur atoms of the nucleophiles used in the present study.

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