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Thermal Profile and Decomposition Kinetics of Some Synthesized 1,5- Benzodiazepines

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Abstract: Thermal analysis of some 1,5-benzodiazepines derived from quinoline chalcones, have been carried out by TG and DSC techniques. TG data of decomposition have been analysed for the kinetic parameters using Freeman-Carroll method. From the observed curves, various kinetic parameters such as order of degradation (n), energy of activation (E), frequency factor (A) and entropy change (ΔS) have been evaluated. Further, thermal stability of benzodiazepines have been determined, which is found to depend on the type of substituent present in the compounds.
Keywords: Kinetic parameters, thermal stability, TGA, DSC, benzodiazepines.

Introduction

Studies on thermal properties of substances can be studied by various thermal techniques which are among the most powerful experimental tools developed during the last century. These techniques are able to characterize a wide range of materials and material properties. In these techniques, the change in properties of material are followed as a function of temperature when it is heated at constant predetermined rate under specified ambient atmospheric conditions.

Literature survey shows that thermal analysis of various types of compounds such as drugs[1,2], polymers[3,4], nuclear fuel[5], pharma materials[6,7], dyes[8,9], fertilizers[10], inorganic[11,12] and organic[13,14] compounds have been reported. Recently, many investigators[15-19] have studied the thermal properties of various materials. However, the little works have done on the thermal properties of benzodiazepine derivatives [20-23].

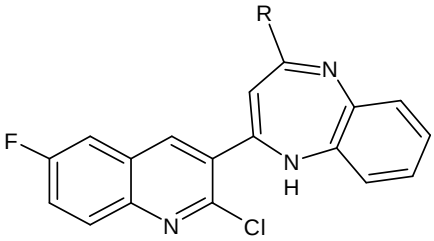
In the present study, thermal properties of some new synthesized benzodiazepines have been reported by DSC and TGA techniques. Using thermograms, various kinetic parameters have also been evaluated.

Experimental

The thermal properties of following benzo-diazepines have been studied.
NBN-1:2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methoxyphenyl)-1*H*-1,5benzodiazepine NBN-2 :4-[2-(2-chloro-6-fluoroquinolin-3-yl)-1*H*-1,5-benzodiazepin-4-yl]aniline NBN-3:4-(4-bromo

phenyl)-2-(2-chloro-6-fluoroquinolin-3-yl)-1*H*-1,5-benzodiazepine
NBN-4 :2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-nitrophenyl)-1*H*-1,5-benzodiazepine
NBN-5 :2-(2-chloro-6-fluoroquinolin-3-yl)-4-(3-nitrophenyl)-1*H*-1,5-benzodiazepine
NBN-6 :4-[2-(2-chloro-6-fluoroquinolin-3-yl)-1*H*-1,5-benzodiazepin-4-yl]phenol
NBN-7 :2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methylphenyl)-1*H*-1,5benzodiazepine
NBN-8 :2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-chlorophenyl)-1*H*-1,5-benzodiazepine
NBN-9 :2-[2-(2-chloro-6-fluoroquinolin-3-yl)-1*H*-1,5-benzodiazepin-4-yl]phenol
NBN-10:2-(2-chloro-6-fluoroquinolin-3-yl)-4-phenyl-1*H*-1,5-benzodiazepine

The common structure of benzodiazepines is:



All these benzodiazepines were recrystallized from ethanol. The purity of compounds was checked by thin layer chromatography and characterization of these compounds was done by IR, NMR spectral data and Mass spectrometry. The physical constants and substituents R of all the synthesized benzodiazepines are given in Table 1.

Instrumentation

Thermo gravimetric analysis (TGA) and Differential Scanning Calorimetry (DSC) measurements were made on the instrument "Pyris-1, Perkin Elmer Thermal Analysis" at the heating rate of 10 ^{o}C/min in nitrogen atmosphere for all the benzodiazepines.

Theory

From TGA curves, various kinetic parameters can be evaluated by Freeman-Carroll[24] equation.

$$\ln (dC/dt)/\ln (1-C) = n-E/R\ [(1/T/(\Delta\ln(1-C)] \quad ...(1)$$

where C is the degree of conversion and is given by

$$C = 1-(W/W_0) \quad \ldots(2)$$

W_0 and W are the initial weight at t=0 and weight at any time t of the material, T is the temperature at absolute scale, n is order of reaction, E is energy of activation and R is gas constant.

A plot of left hand side of eq (1) against (1/T)/(Δln(1-C)) gives a straight line with a slope equal to -E/R and the intercept is equal to n.

The frequency factor A and entropy change ΔS can be determined by the following equations:

$$\ln E - \ln (RT_s^2) = \ln A - \ln\beta - E/RT_s \quad ..(3)$$

$$A = (k_b T / h)\, e^{\Delta S/R} \quad \ldots(4)$$

where T_s is the temperature at which the rate of decomposition is maximum, β is heating rate, k_b is Boltzmann constant and h is Planck's constant.

Results and Discussion

Various thermal properties such as initial decomposition temperature (IDT), the decomposition temperature range and the maximum degradation along with the percentage weight loss and Exo / Endo transitions are reported in Table 2. Further, the experimental melting points are also given in Table 2 for comparison.

For some compounds, degradation is single step process whereas for others, it is multi step process. For NBN-3, NBN-4 and NBN-9, multi step degradation takes place.

Table 2 shows that NBN-10 is unstable whereas NBN-8 is most stable followed by NBN-6. NBN-10 has no side chain or no substitution. While in other compounds, various substituent groups are attached. This suggests that absence of substituent decreases the stability of the present studied compounds. When chloro group is present at para position (as in NBN-8), stability is highest which is followed by the presence of hydroxyl group at para position (as in NBN-6). The presence of other groups also shows significant stability.

Further, Table 2 shows DSC data along with the melting temperature determined by open capillary method. It is observed that the melting temperatures determined by the two methods are in good agreement. The heat of reaction is found to be maximum for NBN-3 and minimum for NBN-5. However, no correlation could be established between heat of reaction, kinetic parameters, melting temperature, thermal stability and substitution group.

Table 1. Physical constants of benzodiazepines.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. ^oC	Yield %
1	**NBN-1**	4-OCH_3-C_6H_4-	$C_{25}H_{17}ClFN_3O$	429.9	0.59	198	54
2	**NBN-2**	4-NH_2-C_6H_4-	$C_{24}H_{16}ClFN_4$	414.9	0.51	175	59
3	**NBN-3**	4-Br-C_6H_4-	$C_{24}H_{14}BrClFN_3$	478.7	0.66	232	49
4	**NBN-4**	4-NO_2-C_6H_4-	$C_{24}H_{14}ClFN_4O_2$	444.8	0.49	202	62
5	**NBN-5**	3-NO_2-C_6H_4-	$C_{24}H_{14}ClFN_4O_2$	444.8	0.64	215	57
6	**NBN-6**	4-OH-C_6H_4-	$C_{24}H_{15}ClFN_3O$	415.8	0.74	248	61
7	**NBN-7**	4-CH_3-C_6H_4-	$C_{25}H_{17}ClFN_3$	413.9	0.82	186	55
8	**NBN-8**	4-Cl-C_6H_4-	$C_{24}H_{14}Cl_2FN_3$	434.4	0.59	232	52
9	**NBN-9**	2-OH-C_6H_4-	$C_{24}H_{15}ClFN_3O$	415.8	0.63	177	58
10	**NBN-10**	C_6H_5-	$C_{24}H_{15}ClFN_3$	399.8	0.70	182	62

* Ethyl acetate:Hexane: 2:8

Table 2. TGA/DSC data for synthesized compounds.

Comp. Code	Amt. mg.	Initial Decomp. Temp. ^oC	Decomp. range ^oC	% Wt. loss	Residual Wt. Loss mg.	Transition	DSC ^0C	Open capillary method ^0C	ΔH $J.g^{-1}$
NBN-1	4.547	140	140-450	41.11	1.8693	Endo.	125.58	128	86.70
NBN-2	4.687	150	150-450	37.20	1.7433	Endo.	159.09	160	66.23
NBN-3	10.895	185	185-728	98.00	10.6769	Endo. Exo.	168.57 238.21	232	66.86 188.40
NBN-4	10.7415	181	181-705	94.00	10.0970	Endo. Endo. Exo	90.28 204.53 274.05	202	6.15 26.01 191.2
NBN-5	2.069	173	173-397	92.00	1.9035	Endo.	165.78	165	8.19
NBN-6	1.747	202	202-494	45.00	0.7862	Endo.	227.96	228	102.69
NBN-7	3.253	142	142-500	47.80	1.5549	Endo. Exo.	167.73 223.11	166	65.21 165.18
NBN-8	3.023	277	277-561	51.00	1.5417	Endo.	239.95	232	70.80
NBN-9	1.793	158	158-426	57.50	1.0309	Endo. Endo.	118.20 265.19	117	39.31 98.51
NBN-10	2.392	100	100-496	52.74	1.2615	Endo.	262.90	262	99.87

Various kinetic parameters, such as order of the degradation (n), energy of activation (E), frequency factor (A) and entropy change (ΔS^o) have also been calculated from the thermograms for each step and are reported in Table 3.

It is evident from Table 3 that order of reaction is quite different in different steps for different benzodiazepines. For single step degradation compound, order of reaction varies from 1.21 to 5.5, whereas for multi steps it varies from 1.6 to 14.

For single step degradation compounds, energy of activation (E) is maximum for NBN-5 and minimum for NBN-8. The frequency factor (A) also varies in the same order. For multi step degradation compounds, In first and second steps, energy of activation is found to be maximum for NBN-9 and minimum for NBN-3. The frequency factor A follows the same order.

Further, change in entropy (ΔS^o) for all these reactions were calculated by equation 4 and are reported in Table 3. These values are both positive and negative for different compounds. The positive values of ΔS^o indicate that the transition state is less ordered than the original compound whereas negative value of ΔS^o corresponds to an increase in the order of transition state than the reactants.

Table 3. The kinetic parameters of benzodiazepine derivatives.

Comp. code	n	E $kJ.mol^{-1}$	A s^{-1}	ΔS $J.mol^{-1}.K^{-1}$
NBN-1	1.25	136.05	5.89 X 1011	128.13
NBN-2	4.63	223.76	7.53 X 1021	322.32
NBN-3 1nd step	9.1	24.704	0.7855	-102.17
NBN-3 2nd step	1.2	340.47	4.18 X 1018	255.33
NBN-4 1st step	14	339.49	2.65 X 1034	562.71
NBN-4 2nd step	6	45.73	87.44	-62.07
NBN-4 3rd step	1.6	241.86	7.81 X 1012	145.62
NBN-5	1.79	556.87	9.87 X 1051	898.37
NBN-6	1.21	138.54	4.87 X 109	86.71
NBN-7	2.68	450.03	2.81 X 1044	754.41
NBN-8	5.5	38.24	241.37	-51.43
NBN-9 1st step	2	667.08	6.3 X 10105	1932.79
NBN-9 2nd step	6.1	94.99	1.92 X 108	106.14
NBN-10	1.78	449.16	1.11 X 1041	688.63

Conclusion

The degradation for some benzodiazepines is multi step process with different order of reaction. Further, thermal stability depends upon the type of substituent present. It is observed that in the studied benzodiazepines, the presence of chloro group (as in NBN-8) increases the stability whereas absence of substituent decreases the stability (as in NBN-10).

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