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Kinetics of dihydro-dibenz[*b*,*f*]azepine derivatives sublimation

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Abstract

Sublimation of dihydro-dibenz[*b*,*f*]azepine derivatives upon heating was studied and confirmed by thermogravimetry (TGA) and differential scanning calorimetry (DSC). DSC was used to analyze thermodynamics of melting. The kinetics of dihydro-dibenz[*b*,*f*]azepine derivatives sublimation were monitored by TGA as a function of temperature. Activation energies of sublimation were deduced and correlated with melting enthalpies and molecular structure. The results indicated that the sublimation was controlled by intermolecular forces in the crystalline lattice of dihydro-dibenz[*b*,*f*]azepine derivatives.

Keywords: Dihydro-dibenz[*b*,*f*]azepine derivatives; Sublimation; Kinetics; Activation energy; Thermogravimetry; Differential scanning calorimetry

1. Introduction

Carbamazepine (Scheme 1) and its analogues including hydrogenated derivatives (Scheme 2) are anticonvulsant compounds useful in the treatment of epilepsy and other neurological disorders [1–4]. Like other conjugated aromatic molecules, such as naphthalene, anthracene, etc., dibenz-azepine derivatives sublime. Re-crystallization by sublimation is a standard method of dibenz-azepines and dihydro-dibenz-azepines purification [4,5]. Phase transitions in solid carbamazepine [6,7], and thermodynamics of sublimation of these bioactive molecules were studied in the past [7–9]. However, to the best of our knowledge, no prior study of azepine derivatives sublimation kinetics and mechanism were published. Most of the work on the benz-azepines derivatives phase change was dedicated to thermodynamics of phase transitions rather than to kinetics and mechanism of their sublimation. To understand effects of molecular structure on sublimation of these molecules, we monitored dihydro-dibenz-azepines sublimation kinetics using thermogravimetry (thermal gravimetric analysis or TGA) [10]. A series of molecules with different substituents were examined (Scheme 2).

Storage stability of compounds of medical interest is important. To establish relative stability of several dihydro-dibenz-azepines, the sublimation rate was monitored at several constant temperatures. The melting enthalpies were found using differential scanning calorimetry (DSC). Activation energies of sublimation and other thermodynamic and kinetic parameters of the dihydro-dibenz-azepine derivatives were deduced.

2. Experimental

All the studied compounds were purchased from Aldrich Chemical Co., at least 98% pure. Thermal gravimetric analysis was conducted in dry nitrogen flow in Thermal Analysis Co., Model 2950 system. Samples of around 3 mg placed in standard platinum cups were used in all TGA measurements. The weight change was monitored isothermally at seven temperatures ranging from 100 to 250 °C with increment of 25 °C, under dry nitrogen flow.

The Thermal Analysis Co., Model 2920 system was used in differential scanning calorimetry (DSC). Samples of around 5 mg were used in sealed aluminum pans. Temperature increase rate was 0.5 K min^{-1} (Fig. 2).

3. Results and discussion

The sublimation can be separated into three consequent and parallel processes: (1) vibrational (thermal) energy transfer into solid, (2) breaking of intermolecular forces in crystal lattice leading to free molecules, (3) vapor transport away from the surface

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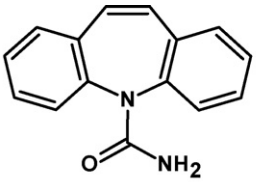


Carbamazepine (5-H-dibenz[b,f]azepine-5-carboxamide)

Scheme 1. Carbamazepine structure.

[11–13]. The kinetics of sublimation may be controlled by the rate of any of these processes. In the presented work, kinetic control by the rate of intermolecular forces dissociation appear to be dominant.

In a steady-state TGA monitoring of sublimation, heat transfer to 3 mg powdered sample was likely fast enough to compensate for the heat loss due to sublimation, as may not be the case in the laser ablation studies [14]. The heat transfer rate to a sample was not likely a rate-limiting step. The evaporated molecules do not contribute to recorded residual weight of the material, and in the presence of cross-cup nitrogen flow vapor does not settle back on the sample. The only reported diffusion-limited sublimation for polycyclic compounds was conducted in high-pressure TGA systems [15,16]. This was not the case in the experiments described here. Sublimation stipulated weight loss was detected even below 100 °C for all of the samples. Least square linear regression was used to deduce the sublimation rate in units of % weight loss per minute.

TGA-detected sublimation kinetics was treated as indicative of the reaction of inter-molecular bonds dissociation, since the dissociation of intermolecular bonds at sublimation temperature appeared to be the rate-limiting in TGA conditions employed here. Time dependence of the sublimate weight change was linear (excluding the initial and final regions) at every temperature and for all of the sublimates studied (Fig. 1). This indicated that, as expected for a bulk rather than monolayer sublimation (desorption), zero-order kinetics was followed over most of the sublimation time (Fig. 1). The first order kinetics is characteristic for sublimation, confirming that sublimation, rather than a chemical reaction [11] or vapor diffusion [8] was a rate-limiting step in weight loss. Indeed, when a solid evaporates, the surface density of the material remains constant, and hence, the rate of evaporation is independent of the surface density of the sublimate [8,17–25].

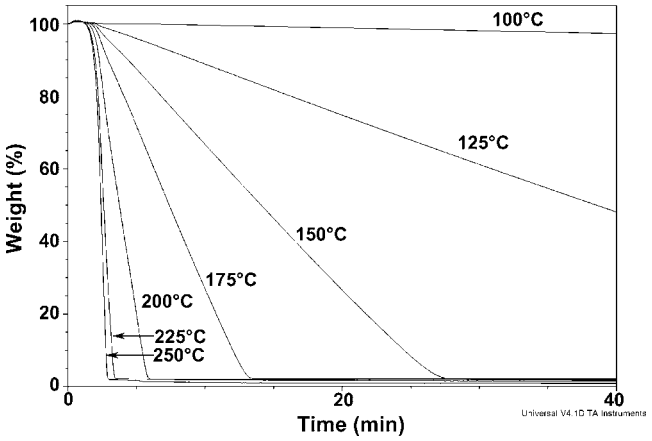
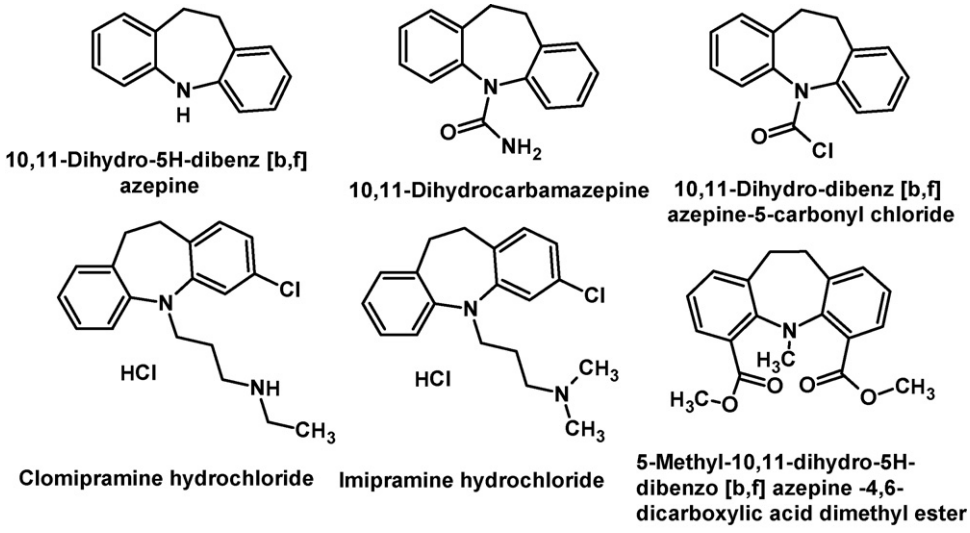


Fig. 1. Typical temperature dependence of dihydro-dibenz-azepine sublimation kinetics monitored by isothermal TGA.

Zero-order kinetics is described in absolute sublimed mass (Eq. (1) and (2)) [17–18] or in relative terms customary for thermal analysis (Eq. (1)) [8,10,11]:

$$r_{\text{subl}} = -\frac{\mathrm{d}m(t)}{m_0\,\mathrm{d}t} = \frac{\mathrm{d}\alpha(t)}{\mathrm{d}t} = k_s(T) = \text{const}_T \quad (1)$$

in integral form, $\alpha(t) = k_s(t)t$, where r_{subl} is a sublimation rate, m_0, and $m(t)$ are the initial mass of subliming solid and the mass after time t from the beginning of sublimation, respectively, $\alpha(t) = (m_0 - m(t))m_0{}^{-1}$, is degree of conversion of the subliming solid at time t [8,10,11,17–19]. The experimental TGA data fits the zero-order linear mass loss model (Eq. (1)) well over most of the monitoring time, indicating correctness of the assumptions that the kinetics was controlled by the rate of sublimation



Scheme 2. Structures of studied dihydro-dibenz-azepine derivatives.

(Fig. 1). Small deviation from the linearity of the weight loss dependence close to the end of sublimation may have been stipulated by evaporation from thin layers described by thin-layer desorption process. The zero-order kinetics was maintained for all the studied molecules at all of the temperatures used.

The slope of relative mass dependence on time of heating (Fig. 1) was used to derive sublimation rate constant (min^{-1}). The temperature dependence of sublimation rate constant can be described by a semi-empirically derived Arrhenius equation. However, Arrhenius equation is strictly speaking, applicable only to gas-phase reactions and should not be used for sublimation description [17–25]. Temperature dependence of sublimation kinetics was described here by theoretically derived Eyring equation applicable to mixed phase reactions as well (Eq. (2)) [17–19]. The equation similar to that of Eyring was first applied by Polanyi and Wigner to sublimation and gas desorption from solids (Eq. (2)) [20–25]. The Eyring equation and Polanyi–Wigner equations are similar in form to that of Arrhenius, but provide a physical meaning to pre-exponential factor and activation threshold energy and take into account a weak temperature dependence of pre-exponential factor and an activation threshold energy [17–19,26]:

$$k_s(T) = F\left(\frac{\nu}{kT}\right) \exp\left(\frac{-E_a}{RT}\right) \quad (2)$$

where $F(\nu/kT)$ is a frequency factor dependent on intermolecular bond vibrations, ν, in solid and absolute temperature, T, E_a is an activation threshold energy (also vibrational frequencies and temperature dependent [17,18,26]), k the Boltzmann's constant and R is the gas constant. Frequency factor can be approximated by a frequency of perpendicular vibration of a molecule on a surface against the bulk of a subliming solid, that is $F(\nu/kT) \approx kT/h = \nu_0 = 6 \times 10^{12}\ s^{-1}$ (h is a Plank's constant) [17–26]. Considering a weak temperature dependence of the frequency factor, $F(\nu/kT)$, and activation energies, the sublimation rate constants at different temperatures and, consequently, the threshold energies, E_a, were deduced by linear regression of the data with Eq. (2). That is, the "Two-Point" form of the Eq. (2) was used (Eq. (3)). (Fig. 2, Table 1).

$$E_a = \frac{RT_1T_2}{T_1 - T_2} \ln \frac{k_1}{k_2} \quad (3)$$

where $R = 8.31\ J\,mol\,K^{-1}$ is a gas constant, $T_1 = 373\ K$, $T_2 = 523\ K$, and k_1 and k_2 are the rate constants deduced at the temperatures T_1, and T_2, using the data of the linear regression line (Fig. 2). Although non-linear forms of regression are preferable as non-distorting Gaussian error distribution [27], linear regression was sufficient for the comparison of the dibenzazepine derivatives sublimation thresholds.

Melting enthalpies, ΔH_m, were derived using DSC of samples in sealed pans, precluding sublimation (Fig. 3). There was a reasonable linear correlation between the melting enthalpy and activation energy of sublimation (Fig. 4). This was expected considering that the same intermolecular forces must be overcome for melting and sublimation to occur. Melting enthalpy values measured by us (Table 1) were of the same order of magnitude as those reported for similar compounds [9,28–31].

According to Hess's cycle [18],

$$E_{a\,sublimation} \geq \Delta H_{sublimation} = \Delta H_{melting} + \Delta H_{evaporation}$$

Indeed, the values of sublimation enthalpies reported for polycyclic aromatic compounds and for some azepines were, on the average, similar or slightly lower than sublimation activation energies found here (Table 1) [5,7–9,30,31]. This indicated that the outlined TGA approach yielded reasonable kinetic parameters for the sublimation process under the assumption of rate control by the rate of breaking of intermolecular, Van der Waals, bonds in crystal lattice [32–34].

Only a weak correlation, if any, of sublimation activation energy with the molecular weight was observed (Fig. 5). Similarly, correlation of melting enthalpies and molecular weight was weak (Fig. 6). In comparison, linear hydrocarbons exhib-

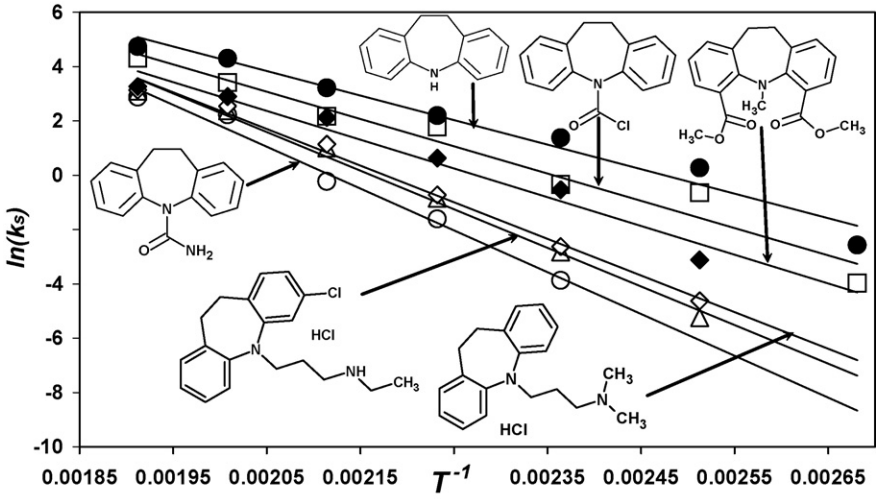
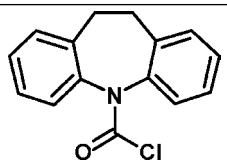
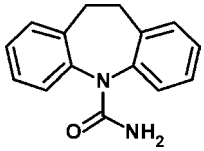
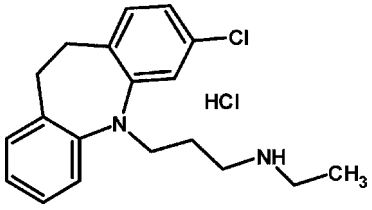
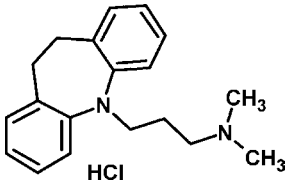
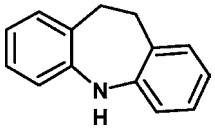
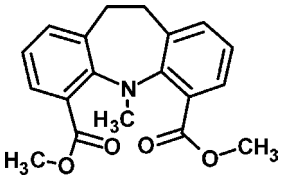


Fig. 2. Temperature (K) and molecular structure dependence of sublimation rate constants (min^{-1}): (●) iminodibenzyl; (□) dihydrodibenzazepine carbonyl chloride; (♦) 5-methyl-10,11-dihydro-5H-dibenzo [b,f] azepine-4,6-dicarboxylic acid dimethyl ester; (◊) imipramine hydrochloride; (△) clomipramine hydrochloride; (○) dihydrocarbamazepine.

Table 1
Molecular structure effect on activation energy of sublimation, E_a, and enthalpy of melting, ΔH_m

Compound name	Structure	Activation energy, E_a (kJ mol^{-1})	Melting enthalpy, ΔH_m (kJ mol^{-1})
Dihydrodibenzazepine carbonyl chloride; Mol. Wt. = 257.71		75.45	25.132
Dihydrocarbamazepine; Mol. Wt. = 238.28		115.70	33.312
Clomipramine hydrochloride; Mol. Wt. = 351.31		106.80	39.768
Imipramine hydrochloride; Mol. Wt. = 316.87		101.34	33.081
Iminodibenzyl; Mol. Wt. = 195.26		67.84	22.592
5-Methyl-10,11-dihydro-5H-dibenzo [*b*,*f*] azepine-4,6-dicarboxylic acid dimethyl ester; Mol. Wt. = 325.37		79.57	29.348

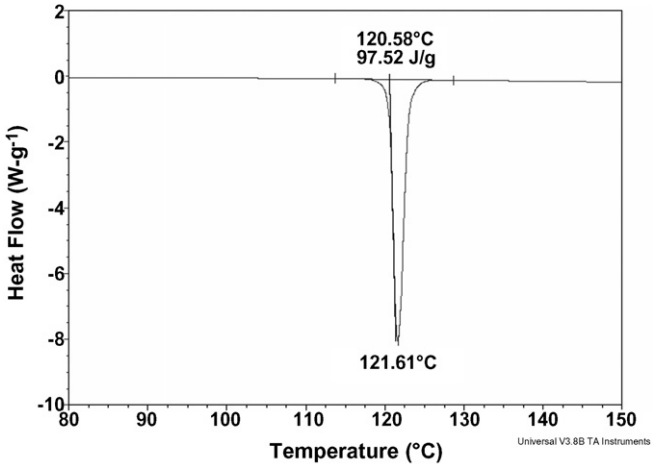


Fig. 3. Typical DSC curve for substituted dihydro-dibenz-azepine.

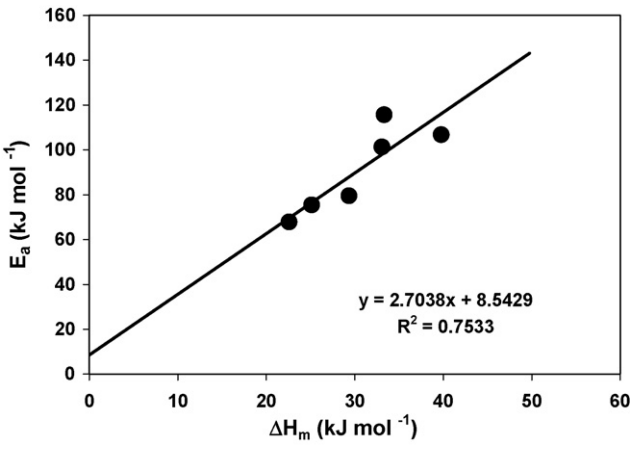


Fig. 4. Correlation between TGA-derived activation energy of sublimation and DSC determined melting enthalpy. *R* is correlation coefficient.

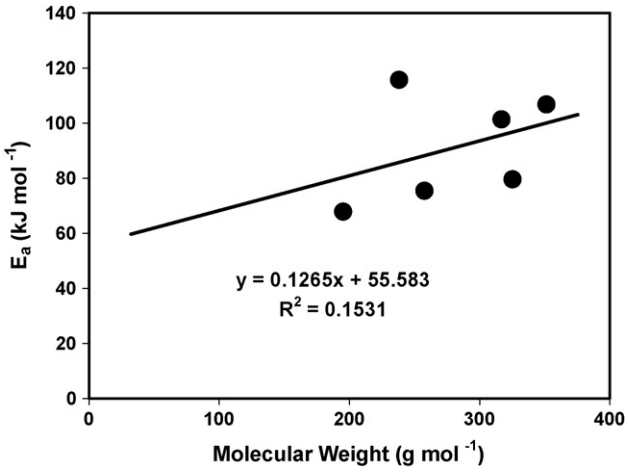


Fig. 5. Molecular weight dependence of activation energy of sublimation. *R* is correlation coefficient.

ited a linear decrease of vapor pressure and increase in enthalpy of melting and evaporation with molecular weight increase [28–31].

Molecular diffusion rate also decreases with molecular weight increase, decreasing the rate of evaporation and contributing to molecular weight-dependent sublimation [18,32]. Unlike sublimation and evaporation, diffusion rate in a gas phase is only weakly dependent on intermolecular forces. Weak dependencies of melting enthalpy and sublimation activation energy on molecular weight (Figs. 5 and 6) indicated that dibenzdihydro-azepines sublimation and melting was controlled by Van der Waals interactions in the crystalline lattice rather than by the rate of vapor removal [32–34].

The values of sublimation activation energies of the studied dihydro-dibenz-azepines can be separated into two groups: those containing nitrogen in the substituent group, and those without (Fig. 3, Table 1). The difference is significant, 124.1, 108.8, and 106.1 kJ mol^{-1} for those with amino group relative to 61.76, 69.90, and 85.48 kJ mol^{-1} to those without. One can speculate about the strength of intermolecular interactions in systems with amines, which are strong electron-donors and form

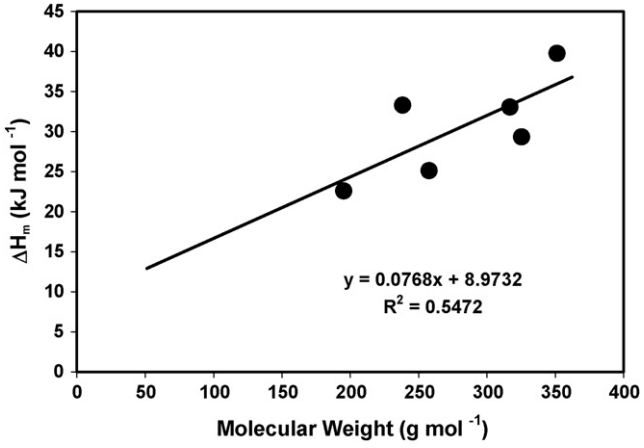


Fig. 6. Molecular weight dependence of melting enthalpy. *R* is correlation coefficient.

strong hydrogen bonds [35]. Charge transfer complex formation between amino-functional and aromatic molecules was also reported [36,37]. Further experimental and theoretical studies are required to explain the observed difference.

4. Conclusions

The sublimation rates of a series of dihydro-dibenz-azepines were monitored by TGA as a function of temperature. The activation energies of the sublimation were deduced. DSC was used to measure heats of melting for the same compounds. It was found that there was only weak dependence of the sublimation activation energies and melting enthalpies on molecular weight of studied azepines. This suggested that sublimation of azepines was controlled by intermolecular interactions. Observation of higher activation energies of azepines containing, in the side chain substituent an amino-group capable of strong Van der Waals interactions and charge-transfer complex formation supported the above conclusion. Detailed molecular modeling and further experimental work is required to confirm the conclusions.

Acknowledgement

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