

An Examination of the Thermodynamics of Fusion, Vaporization, and Sublimation of (R,S)- and (R)-Flurbiprofen by Correlation Gas Chromatography

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Received 20 January 2012; revised 31 January 2012; accepted 7 February 2012

Published online 12 March 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23094

ABSTRACT: The vaporization, fusion, and sublimation enthalpies of (R,S)- and (R)-flurbiprofen at $T = 298.15$ K are reported and compared with literature values when available. Correlation gas chromatography experiments were first performed to identify appropriate standards that could be used for materials containing a single fluorine substituent. Subsequent correlations resulted in a vaporization enthalpy for (R,S)-flurbiprofen and (R)-flurbiprofen, $\Delta H_{\text{vap}}(298.15 \text{ K})$, of (127.5 ± 5.5) and (127.4 ± 4.7) kJ mol⁻¹, respectively. Fusion enthalpies, $\Delta H_{\text{fus}}(387 \text{ K})$, of $(28.2 \pm \text{and}, \Delta H_{\text{fus}}(381 \text{ K}))$, $(22.8 \pm \text{kJ mol}^{-1})$ were also measured by differential scanning calorimetry for the racemic and chiral forms of flurbiprofen. Adjusted to $T = 298.15$ K and combined with the vaporization enthalpy resulted in sublimation enthalpies, $\Delta H_{\text{sub}}(298.15 \text{ K})$, of (155.6 ± 5.8) and (145.1 ± 5.7) kJ mol⁻¹ for (R,S)- and (R)-flurbiprofen, respectively. The fusion enthalpy measured for the racemic form was in excellent agreement with the literature value, while the sublimation enthalpy varies substantially from previous work. Two weak solid–solid phase transitions were also observed for (R)-flurbiprofen at $T = 353.9$ K (0.30 ± 0.1) and 363.2 K (0.21 ± 0.03) kJ·mol⁻¹. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 101:2045–2054, 2012

Keywords: flurbiprofen; sublimation; vaporization; fusion enthalpies; chirality; gas chromatography; calorimetry (DSC); cancer; physical characterization; thermodynamics

INTRODUCTION

(R,S)-Flurbiprofen (Ansaid™ (Pfizer, NY, NY), Urbifen™ (General Pharmaceutical, Dhaka, Bangladesh), and Flurwood™ (W. Woodward, Karachi Pakistan)), [(±) 2-fluoro- α -methyl-1,1'-biphenyl]-4-acetic acid, administered in racemic form is an anti-inflammatory nonsteroidal drug used to relieve pain, stiffness, swelling, and tenderness in osteoarthritis and rheumatoid arthritis.¹ The R isomer, (–)-flurbiprofen (tarenflurbil (Flurizan™, Myriad Pharmaceutical, Salt Lake City, UT)), inhibits an enzyme responsible for amyloid beta synthesis, but recent phase three trials have found it to be ineffective in retarding Alzheimer's disease.² It has also been of interest in prevention of prostate and gastric

cancers.^{3,4} The structure of the R isomer is shown in Figure 1. Several thermodynamic properties including the sublimation enthalpy, melting temperature, vapor pressure over a limited range of temperature, and enthalpy of fusion have recently been reported for the (R,S) form in the literature. Available literature data as well as some recent work are summarized in Table 1.^{5–7} Three different crystalline modifications have been reported for (R,S)-flurbiprofen.⁷ Modification II was obtained by cooling the melt following a differential scanning calorimetry (DSC) experiment or by rapid crystallization from heptane to -18°C . It is reverted back to the most stable form by heating. The commercial product has been reported to be most stable polymorph.⁷ The thermal properties of the R isomer, (–)-flurbiprofen, do not appear to have been reported in the literature.

Availability of both the sublimation and fusion enthalpy of (R,S)-flurbiprofen allows an evaluation of the compound's vaporization enthalpy. This can be achieved using the thermodynamic equality described

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Journal of Pharmaceutical Sciences, Vol. 101, 2045–2054 (2012)

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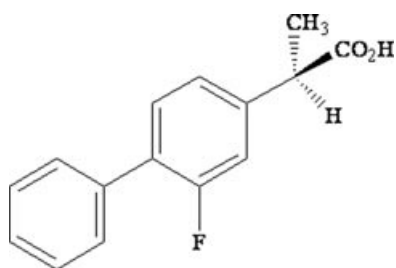


Figure 1. (R)-(-)-Flurbiprofen.

in Eq. 1. Evaluation of the vaporization enthalpy at $T = 298.15$ K requires both sublimation and fusion enthalpies to be adjusted for temperature. Protocols for the temperature adjustment of both have been developed and are summarized in Eqs. 2 and 3.⁹

$$\Delta H_{\text{vap}}(298\text{K}) = \Delta H_{\text{sub}}(298\text{K}) - \Delta H_{\text{fus}}(298\text{K}) \quad (1)$$

$$\begin{aligned} \Delta H_{\text{sub}}(298.15\text{K})/(\text{kJ mol}^{-1}) &= \Delta H_{\text{sub}}(T_m) \\ &+ \{0.75 + 0.15C_p(c)/[\text{J}/(\text{mol}^{-1}\text{K}^{-1})]\} \\ &\times (T_m - 298.15)/1000 \end{aligned} \quad (2)$$

$$\begin{aligned} \Delta H_{\text{fus}}(298\text{K})/\text{kJ mol}^{-1} &= \Delta H_{\text{fus}}(T_m) \\ &+ [0.15C_p(c) - 0.26C_p(l) - 9.93] \\ &\times [T_{\text{fus}} - 298.15]/1000 \end{aligned} \quad (3)$$

The terms $C_p(l)$ and $C_p(c)$ in Eqs. 2 and 3 represent the heat capacity of the liquid and solid at $T = 298.15$ K, respectively. Both $C_p(c)$ and $C_p(l)$ were estimated by group additivity.⁹ The vaporization enthalpy evaluated by this procedure is also provided in Table 1. Although estimations of sublimation enthalpies can be problematic because of differences in packing, rough estimations of vaporization enthalpy is considerably less so. These estimations are useful in providing the experimentalist a rough value as a guide and can be helpful in identifying problematic values or unusual intermolecular interactions. As an example, the vaporization enthalpy calculated for flurbiprofen in Table 1 of 88.4 ± 1.9 kJ mol⁻¹ at $T = 298.15$ K using experimental values and Eqs. 1–3 can be compared with a value of 102.8 kJ mol⁻¹ estimated

for biphenyl-4-carboxylic acid and 112.2 kJ mol⁻¹ estimated for α -methyl-4-biphenylacetic acid using the following simple equation:

$$\Delta H_{\text{vap}}(298\text{K})/\text{kJ mol}^{-1} = 4.69n_c + b + 3.0 \quad (4)$$

where n_c represents the number of carbon atoms and b represents the group value for a carboxylic acid (38.8).¹⁰ If the experimental sublimation enthalpy of 127.5 kJ mol⁻¹ at $T = 298.15$ K is used for biphenyl-4-carboxylic acid⁸ in conjunction with the experimental fusion enthalpy measured in this work and adjusted to $T = 298.15$ K, a vaporization enthalpy of approximately $\Delta H_{\text{vap}}(298\text{K}) = 107.5$ kJ mol⁻¹ is calculated. This value is in good agreement with the value estimated using Eq. 3 above. The value for biphenyl-4-carboxylic acid is approximate because of the large temperature adjustment required both in adjustments of its fusion enthalpy (12.1 kJ mol⁻¹) and in the drop calorimetric method used in the measurement of its sublimation enthalpy (46.4 kJ mol⁻¹).⁸ Estimates of both these compounds are considerably larger than the experimental value of (88.4 ± 1.9) kJ mol⁻¹ reported in Table 1 at $T = 298.15$ K for (R,S)-flurbiprofen. This article reports the fusion, vaporization, and sublimation enthalpies of both (R,S)- and (R)-flurbiprofen obtained by a combination of DSC and correlation gas chromatographic measurements and compares the results to the current literature value.

Correlation gas chromatography is a simple method for evaluating vaporization enthalpy regardless of whether the target substance is a solid or liquid, provided appropriate standards are available with reliable vaporization enthalpies.^{11–16} The standards are injected simultaneously with the target substance(s) along with an unretained analyte, which measures elution time. As each analyte moves on the column according to its vapor pressure on the column, measurement of the temperature dependence of its adjusted retention time, t_a , provides a convenient measure of both its volatility and interaction with the column. The adjusted retention time is evaluated as the difference between the measured retention time of each analyte and that of a nonretained

Table 1. Sublimation, Fusion, and Vaporization Enthalpies of (RS)-Flurbiprofen and Biphenyl-4-Carboxylic Acid

	$\Delta H_{\text{sub}}(T_m)$ (kJ mol ⁻¹)	T_m (K)	$\Delta H_{\text{fus}}(T)$ (kJ mol ⁻¹)	T/K	$C_p(l)/C_p(c)$ [J/(mol ⁻¹ K ⁻¹)]	$\Delta H_{\text{vap}}(298\text{K})$ (kJ mol ⁻¹)	References
(R,S)-flurbiprofen	108.4 ± 0.5	359.7					5
	110.2 ± 0.5	298.2					6
			27.9 ± 0.2	387.7	396.5/297.5		7
Biphenyl-4-carboxylic acid			21.8 ± 1.8	298.15		88.4 ± 1.9	7
			32.1 ± 0.2	499.5	329.5/236.1		TW ^a
	127.5 ± 4.1	298.2	20.0 ± 3.6^a	298.2		107.5 ± 5.5	8

^aThis work, see the section *Fusion Enthalpies*.

reference. Since the vapor pressure of each analyte of the column is inversely proportional to its adjusted retention time, t_a , a plot of $\ln(t_0/t_a)$ versus $1/T$ run isothermally, usually over a $T = 30$ K range, results in a linear relationship with a slope equal to the negative of the enthalpy of transfer of the analyte from the column to the gas phase, $\Delta H_{\text{trn}}(T)$, divided by the gas constant. The term t_0 refers to a reference time, 1 min, and t_a is the time each analyte spends on the column. The enthalpy of transfer can be related to the following thermodynamic relationship:

$$\Delta H_{\text{trn}}(T_m) = \Delta H_{\text{vap}}(T_m) + \Delta H_{\text{intr}}(T_m) \quad (5)$$

where $\Delta H_{\text{vap}}(T_m)$ refers to the vaporization enthalpy and $\Delta H_{\text{intr}}(T_m)$ refers to the interaction of each analyte with the column measured at some mean temperature, T_m . The enthalpy of transfer, $\Delta H_{\text{trn}}(T_m)$, has been found to correlate linearly with $\Delta H_{\text{vap}}(T)$. A study of how the magnitude of $\Delta H_{\text{trn}}(T_m)$ compares with $\Delta H_{\text{vap}}(T_m)$ both measured at T_m suggests that the $\Delta H_{\text{vap}}(T_m)$ makes the largest contribution to $\Delta H_{\text{trn}}(T_m)$.¹⁴ Temperature T usually differs from T_m and has usually been the reference temperature, 298.15 K.

The quality of the correlation obtained is determined both by the quality of data available for the standards and selection of the appropriate standards. Selection of the proper standards is of paramount importance. Previous work has demonstrated that an ether oxygen can be substituted for a methylene group.^{13,17} In view of the few monofluorinated aromatic compounds whose vaporization enthalpies have been measured,¹⁸ we decided first to examine whether a surrogate substituent could be identified for this group. As fluorine is frequently substituted for hydrogen in other applications, our first approach was to examine if substitution of a single fluorine atom for hydrogen on a medium size aromatic hydrocarbon would correlate with the parent hydrocarbon. The rationale for this approach was based on the relatively small contribution that a single fluorine generally contributes to the vaporization enthalpy as a single substituent on an aromatic carbon atom (1.2 kJ mol⁻¹).¹⁰

MATERIALS AND METHODS

All compounds used in this study were purchased from Sigma–Aldrich Chemical Company (Milwaukee, Wisconsin; and St. Louis, Missouri) and used as purchased. All materials had stated purities by the supplier of 99 % mass fraction or better except 2-fluorobenzoic acid and biphenyl-4-carboxylic acid with stated purities of 97% and 95%, respectively. The flurbiprofens (CAS 5104-49-4) were of pharmaceutical

grade. Correlation gas chromatography experiments were performed on an HP 5890 Gas Chromatograph (Santa Clara, California) equipped with a flame ionization detector and run at a split ratio of approximately 100/1. Retention times were recorded on an HP Chemstation. The compounds were run isothermally on a 0.25 mm, 30 m DB5 MS column at 10 psi using helium as the carrier gas. Loading on the column was kept to a minimum by injecting 1 μ L of a dilute solution of the analytes in methanol. Although enthalpies of transfer do depend on the nature of the column and the various instrumental parameters such as flow rate and temperature used, the results following the correlation remain independent of the experimental conditions provided they remain constant within the reproducibility of the results. At the temperatures of these experiments, the retention time of methanol also functioned as the nonretained reference. Adjusted retention times, t_a , were calculated by subtracting the measured retention time of the nonretained reference from the retention time of each analyte as a function of temperature, at $T = 5$ K intervals over a $T = 30$ K range. Column temperatures were controlled by the gas chromatograph and were monitored independently by using a Fluke 50S K/J digital thermometer (Everett, Washington). The temperature maintained by the gas chromatograph was constant to ± 0.1 K. Enthalpies of transfer were calculated as the product of the slope of the line obtained by plotting $\ln(t_0/t_a)$ versus $1/T$ and the gas constant, R . All plots of $\ln(t_0/t_a)$ versus $1/T$, where $t_0 = 1$ min, were characterized by correlation coefficients, $r^2 > 0.99$. The uncertainties ($\pm\sigma$) reported in the last column of the correlation tables below were calculated from the uncertainty in the slope and intercept of the equations listed at the bottom of each respective run. These uncertainties reflect the potential error in the absolute value of the vaporization enthalpy and are a measure of the precision of the measurements. Although the results are highly reproducible, the absolute error is also dependent on the quality of the data used as reference. The uncertainties associated with the temperature adjustments are as follows. A potential uncertainty equal to 30% of the correction is usually associated with the use of Eqs. 2 and 3. Although this value has been chosen arbitrarily, the combination of Eqs. 2 and 3 has been shown to fit experimental sublimation enthalpies within an uncertainty of approximately ± 4 kJ mol⁻¹.¹⁸ The uncertainty associated with Eq. 6., described below, has an uncertainty of ± 16 J mol⁻¹ assigned to the temperature-independent term of the equation.⁹ Equations 2, 3, and 6 have proven reliable up to approximately 500 K, although the uncertainties associated with temperature adjustments near the upper limit are probably larger.

Table 2. Retention Times of Several Alkanes and Some 1-Fluoro Derivatives

Run 1	<i>T</i> (K)						
	<i>t</i> (min)						
	409.1	414.1	419.2	424.2	429.3	434.3	439.3
Methane ^a	3.124	3.152	3.175	3.199	3.227	3.249	3.273
Heptane ^b	3.508	3.504	3.503	3.499	3.501	3.502	3.509
1-Fluoroheptane	3.910	3.860	3.819	3.780	3.752	3.727	3.712
Decane	5.097	4.888	4.725	4.593	4.445	4.330	4.241
Dodecane	8.809	8.022	7.394	6.855	6.391	6.005	5.680
1-Fluorododecane	14.552	12.776	11.416	10.233	9.237	8.402	7.684
Tetradecane	19.310	16.648	14.603	12.868	11.400	10.199	9.179
1-Fluorotetradecane	35.568	29.758	25.444	21.764	18.710	16.216	14.094

^aNonretained reference.^bUsed as the solvent.

Gas Chromatographic Retention Times

The experimental gas chromatographic retention times for one of the runs performed for each set of correlations is provided below. All runs were conducted in duplicate, to confirm reproducibility except for (R)-flurbiprofen. This material exhibited the same retention times as the racemic form. The resulting vaporization enthalpies of both runs were used to generate statistics listed below. As described below, the runs

using alkanes and 1-fluoroalkanes were performed to establish whether alkanes can successfully be used to evaluate the vaporization enthalpies of compounds containing a single fluorine substituent.

Fusion Enthalpies

The fusion enthalpies of (R,S)- and (R)-flurbiprofen were measured on a PerkinElmer DSC 7 instrument (Waltham, Massachusetts) using the Pyris Series

Table 3. Retention Times of Some Carboxylic Acids and (R,S)-Flurbiprofen

Run 3	<i>T</i> (K)						
	<i>t</i> (min)						
	454.2	459.2	464.1	469.1	474.1	479.2	484.1
Methanol ^a	3.140	3.164	3.178	3.193	3.215	3.235	3.251
4-Fluorobenzoic acid	3.866	3.813	3.756	3.710	3.680	3.655	3.630
2-Fluorobenzoic acid	4.056	3.980	3.901	3.837	3.793	3.755	3.720
4-Methoxybenzoic acid	5.756	5.448	5.166	4.934	4.747	4.589	4.452
4- <i>t</i> -Butylbenzoic acid	6.704	6.273	5.854	5.515	5.242	5.017	4.823
Ibuprofen	9.151	8.311	7.561	6.952	6.457	6.048	5.704
Hexylbenzoic acid	13.987	12.349	10.893	9.731	8.788	8.016	7.377
Octylbenzoic acid	28.291	23.993	20.363	17.486	15.179	13.315	11.798
(R,S)-Flurbiprofen	33.882	28.571	24.089	20.558	17.723	15.442	13.58

^aNonretained reference and solvent.**Table 4.** Retention Times of Some Carboxylic Acids and (R)-Flurbiprofen

Run 5	<i>T</i> (K)						
	<i>t</i> (min)						
	454.3	459.2	464.2	469.2	474.2	479.2	484.2
Methanol ^a	3.06	3.086	3.083	3.112	3.133	3.159	3.175
4-Fluorobenzoic acid	3.812	3.755	3.682	3.65	3.618	3.598	3.574
2-Fluorobenzoic acid	3.997	3.916	3.824	3.774	3.728	3.696	3.662
4-Methoxybenzoic acid	5.69	5.367	5.074	4.858	4.672	4.521	4.387
4- <i>t</i> -Butylbenzoic acid	6.599	6.126	5.722	5.41	5.149	4.931	4.743
ibuprofen	9.03	8.157	7.42	6.838	6.354	5.955	5.616
Hexylbenzoic acid	13.846	12.094	10.695	9.565	8.649	7.887	7.259
Biphenyl-4-carboxylic acid	22.085	18.918	16.358	14.309	12.629	11.261	10.12
Octylbenzoic acid	28.139	23.596	20.078	17.246	14.971	13.12	11.627
(R)-Flurbiprofen	33.617	28.084	23.743	20.261	17.474	15.204	13.375

^aNonretained reference and solvent.

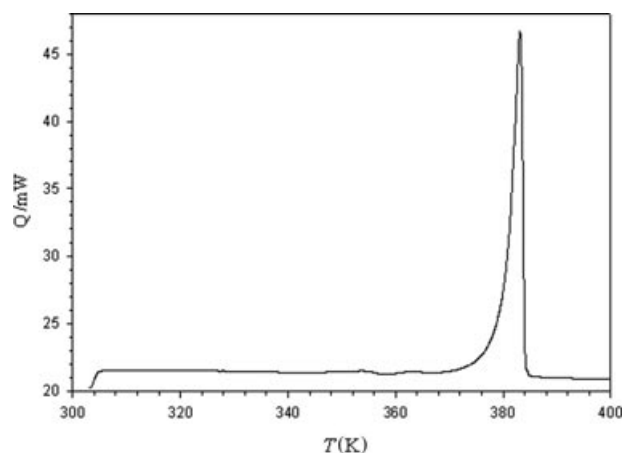


Figure 2. The DSC curve of (R)-(-)-flurbiprofen. Weak solid–solid transitions are observed at $T = 353.9$ and 363.9 K.

Thermal Analysis software. The experiments were conducted under an atmosphere of nitrogen at a flow rate of 20 mL/min at a ramp rate of $5^{\circ}\text{C}/\text{min}$ from $T = 298$ K to T_{fus} in hermetically sealed aluminum pans. The instrument was calibrated using indium metal, 99.999%, as a standard. The results are summarized in Table 4. Fusion temperatures are reported as onset temperatures. No mass loss was observed following fusion. The fusion enthalpy for (R,S)-flurbiprofen was performed as a means of confirming the identity of the crystalline modification used. Agreement of this work with the literature was very good. A single endothermic peak was observed with an onset temperature of $T = (387.1 \pm 0.1)$ K. Upon a second heating of the supercooled melt, (R,S)-flurbiprofen exhibited an exothermic crystallization peak at approximately $T = 317$ K and a second weaker exothermic peak due to a phase transition at $T = 338$ K, similar to what has been previously observed.⁷ The fusion enthalpy and onset temperature measured were nearly identical to the initial results, suggesting that the sample reverted back to the more stable polymorph upon heating.

The DSC behavior of (R)-flurbiprofen was somewhat different. It showed weak broad transitions centered at $T = (353.9 \pm 0.1$ and $363.7 \pm 0.1)$ K followed by fusion at an onset temperature of $T = (380.6 \pm 0.4)$ K (Fig. 2). This material was also found to supercool following fusion when rapidly cooled to room temperature in the DSC. It was observed to solidify exothermically upon reheating to approximately $T = 313$ – 333 K or if cooled in the DSC at 5 K/min from its melting temperature. It then melted at its normal fusion temperature. The weak transitions observed with fresh samples were not obvious upon remelting. The DSC heating curve of a mixture of the R isomer with the racemic form in a ratio of 5.16/3.67 mg, respectively, resembled a superimposition of the

two pure components. Upon reheating the melt, which also supercooled, the solidification of both (R,S)- and (R)-flurbiprofen and the phase transition of the (R,S)-form could be observed as illustrated in Figure 3. This suggests that the weak transitions observed in the R isomer are not due to the presence of small amounts of its racemate. The ideal fusion enthalpy calculated for the mixture based on the composition of the pure materials is 25.2 ± 0.2 kJ mol⁻¹ and can be compared with a total value of 24.2 kJ mol⁻¹ measured experimentally (single determination). Upon prolonged standing, both materials solidified and no exothermic phase transitions were observed.

The fusion temperature of biphenyl-4-carboxylic acid is at the limit of applicability of Eq. 3. The uncertainty assigned to the temperature adjustment is likely to be a minimum value. Additionally, the uncertainty associated with the reported sublimation enthalpy of biphenyl-4-carboxylic acid is a measure of the precision of the measurement made by Calvet drop calorimetry at $T = 488$ K.⁸ It does not include any uncertainty associated with the 46.4 kJ mol⁻¹ temperature adjustment to $T = 298.15$ K applied to the measurements. For these reasons, the vaporization enthalpy of biphenyl-4-carboxylic acid, included in one of the mixtures, was not used as a standard.

Sublimation, Fusion, and Vaporization Enthalpies of the Standards

Literature values for the sublimation fusion and vaporization enthalpies of the standards used in this

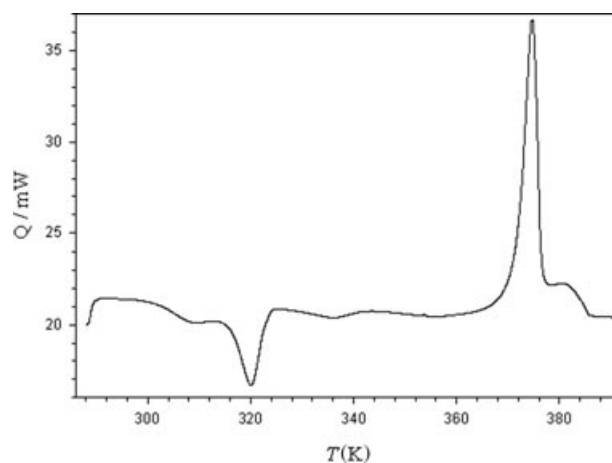


Figure 3. The DSC trace of the cooled melt of a mixture of (R)-flurbiprofen (5.16 mg) and the racemic mixture (3.67 mg). The exothermic peaks at $T = 310$ and 320 K represent solidification of the supercooled liquid and the exothermic peak at 338 K represents the phase change associated with the (R,S) form. The endothermic peaks at $T = 374$ and 381 K are associated with fusion of the (R)- and (R,S)- mixture.

Table 5. Fusion Enthalpies of (R,S)-, (R)-(-)-Flurbiprofen, and 2-Fluorobenzoic Acid

	Sample (mg)	$\Delta H_{\text{trns}}(T)$ (kJ mol ⁻¹)	T_{trns} (K) peak	$\Delta H_{\text{fus}}(T_{\text{fus}})$ (kJ mol ⁻¹)	T_{fus} (K) onset	$\Delta H_{\text{fus}}(T_{\text{fus}})_{\text{av}}$ (kJ mol ⁻¹)	$T_{\text{fus}}(\text{K})_{\text{av}}$ onset
(R,S)-Flurbiprofen	7.12			27.9	387.1	28.2 ± 0.3	387.1 ± 0.1
	7.60			28.4	387.2		
	7.60			27.4 ^a	386.0		
(R)-(-)-Flurbiprofen	9.86	0.33/0.19	353.9/363.2	23.2	380.4	23.3 ± 0.3 ^b	380.6 ± 0.4
	10.0	0.39/0.19	353.9/363.6	22.6	380.5		
	10.84	0.19/0.24	353.8/364.2	22.7	381.1		
2-Fluorobenzoic acid	17.76	0.43	309.8	20.2	396.8	20.1 ± 0.1 ^c	397.4 ± 0.9
	17.53	0.41	309.8	20.1	397.0		
	17.24	0.41	309.8	20.1	398.4		
Biphenyl-4-carboxylic acid	15.80			31.9	499.7	32.1 ± 0.2	499.5 ± 0.5
	17.63			32.2	499.8		
	7.67			32.2	498.9		

^aThe fusion enthalpy measured by reheating the melt; not used in evaluating the mean.

^bIncludes the solid–solid transition enthalpies of 0.5 kJ mol⁻¹.

^cIncludes the solid–solid transition enthalpy of 0.42.

study are summarized in Tables 5–8 and their structures are provided in Figure 4. The results have been reported by different groups who used different method for adjusting their results to a common reference temperature. For consistency, all of the compounds were adjusted from the mean temperature of measurement to $T = 298.15$ K using Eqs. 1–3 and 6

as appropriate.

$$\begin{aligned} \Delta H_{\text{vap}}(298\text{K})/\text{kJ mol}^{-1} = \\ \Delta H_{\text{vap}}(T_m) + [10.58 + 0.26C_p(l)] \\ \times (T_m - 298.15)/1000 \end{aligned} \quad (6)$$

Table 6. Adjustment of Literature Sublimation Enthalpies to $T = 298.15$ K^a

Compound	$\Delta H_{\text{sub}}(T_m)$ (kJ mol ⁻¹)	T_m (K)	$C_p(c)$ [J mol ⁻¹ K ⁻¹]	$\Delta H_{\text{sub}}(298\text{K})^a$ (kJ mol ⁻¹)	References
4-Fluorobenzoic acid	91.2 ± 1.3	370	164.9	93.4 ± 2.4	19
2-Fluorobenzoic acid	93.9 ± 0.5	316.2	164.9	94.8 ± 0.5 ^b	20
4-Methoxybenzoic acid	110.60 ± 0.3	351.3	226.5	112.5 ± 0.6	21
4- <i>t</i> -Butylbenzoic acid	103.8 ± 0.42	334.1	244.9	105.2 ± 0.6	22
4-Hexylbenzoic acid	119.9 ± 0.22	355.1	311.2	122.6 ± 0.8	23
Biphenyl-4-carboxylic acid				127.5 ± 4.1	8
4-Octylbenzoic acid	130.9 ± 1.0	369.7	365	140.7 ± 1.6 ^c	23

^aTemperature adjustments using Eq. 2.⁸

^bIncludes the enthalpy of solid–solid phase transitions at $T = 309.8$ K, (0.41 ± 0.1) kJ mol⁻¹ and a temperature adjustment of (0.46 ± 0.1) kJ mol⁻¹.

^cIncludes the enthalpy of solid–solid phase transitions at $T = [305.6$ K, (5.40 ± 0.1) kJ mol⁻¹ and 366.6 K, (0.47 ± 0.03) kJ mol⁻¹] and a temperature adjustment of 4.0 kJ mol⁻¹.

Table 7. Adjustment of Literature Fusion Enthalpies to $T = 298.15$ K

Compound	$\Delta H_{\text{fus}}(T_{\text{fus}})$ (kJ mol ⁻¹)	T_{fus} (K)	$C_p(l)/C_p(c)$ [J mol ⁻¹ K ⁻¹]	$\Delta H_{\text{fus}}(298\text{K})^a$ (kJ mol ⁻¹)	References
4-Fluorobenzoic acid	20.9	451.2	221.4/164.9	14.4 ± 2.0	24
2-Fluorobenzoic acid	20.1 ± 0.1	397.4	221.4/164.9	16.3 ± 1.3 ^b	TW ^c
4-Methoxybenzoic acid	28.97 ± 1.0	455.3	269.9/226.5	21.74 ± 2.4	25
4- <i>t</i> -Butylbenzoic acid	17.91 ± 0.5	436	323.9/244.9	10.01 ± 2.4	26
4-Hexylbenzoic acid	13.83 ± 0.1 ^d	385.9 ^e	399.6/311.2	7.9 ± 1.8	23
4-Octylbenzoic acid	21.39 ± 0.2 ^f	388 ^e	463.4/365	14.6 ± 2.0	23
Biphenyl-4-carboxylic acid	32.1 ± 0.2	499.5	329.5/236.1	20.0 ± 3.6	TW ^c
(R,S)-Flurbiprofen	27.9 ± 0.2	387.7	396.5/297.5	21.8 ± 1.8	7
(R)-Flurbiprofen	23.3 ± 0.3 ^g	380.6	396.5/297.5	17.7 ± 1.7	TW ^c

^aTemperature adjustments using Eq. 3.

^bIncludes the enthalpy of solid–solid phase transitions at $T_{\text{trns}} = 309.8$ K, (0.41 ± 0.1) kJ mol⁻¹ and a temperature adjustment of (−4.2 ± 1.3) kJ mol⁻¹.

^cThis work.

^dIncludes a liquid crystal to isotopic liquid transition of 0.95 ± 0.04 kJ mol⁻¹.

^eTransition temperature to an isotropic liquid.

^fIncludes a solid–solid phase transitions at $T_{\text{trns}} = [305.6$ K (5.40 ± 0.1) kJ mol⁻¹ and 366.6 K (0.47 ± 0.03) kJ mol⁻¹] and liquid crystal to isotopic liquid transition of 1.2 ± 0.12 kJ mol⁻¹.

^gIncludes the two solid–solid transitions reported in Table 4.

Table 8. Vaporization Enthalpies of the Liquid Standards at $T = 298.15$ K

Compound	$\Delta H_{\text{vap}}(T_m)$ (kJ mol ⁻¹)	T_m (K)	$C_p(l)$ [J mol ⁻¹ K ⁻¹]	$\Delta H_{\text{vap}}(298 \text{ K})^a$ (kJ mol ⁻¹)	References
1-Fluoroheptane	40.4 ± 0.1	308.2	242.5	41.1 ± 0.3	27
<i>n</i> -Heptane				36.6 ± 0.4	28
<i>n</i> -Decane				51.4 ± 0.5	28
1-Fluorododecane	55.9 ± 0.1	393.2	402	66.9 ± 3.3	27
<i>n</i> -Dodecane				61.5 ± 0.6	28
1-Fluorotetradecane	61.1 ± 0.1	418.2	465.8	76.9 ± 4.7	27
<i>n</i> -Tetradecane				71.7 ± 0.7	28
Ibuprofen				106 ± 5.5	17

^aTemperature adjustments using Eq. 6.

RESULTS

The first correlation performed was to examine how well hydrocarbons are able to reproduce the vaporization enthalpies of singly fluorinated hydrocarbon derivatives. The fluorinated compounds chosen were 1-fluorinated alkanes that varied in the size

of the hydrocarbon component, 1-fluoro-heptane, -dodecane, and -tetradecane. Each correlation was repeated twice. The retention times of only one of the duplicate runs is reported in Table 2. The resulting correlation equations of both runs, however, are included in the equations provided below (Table 10).

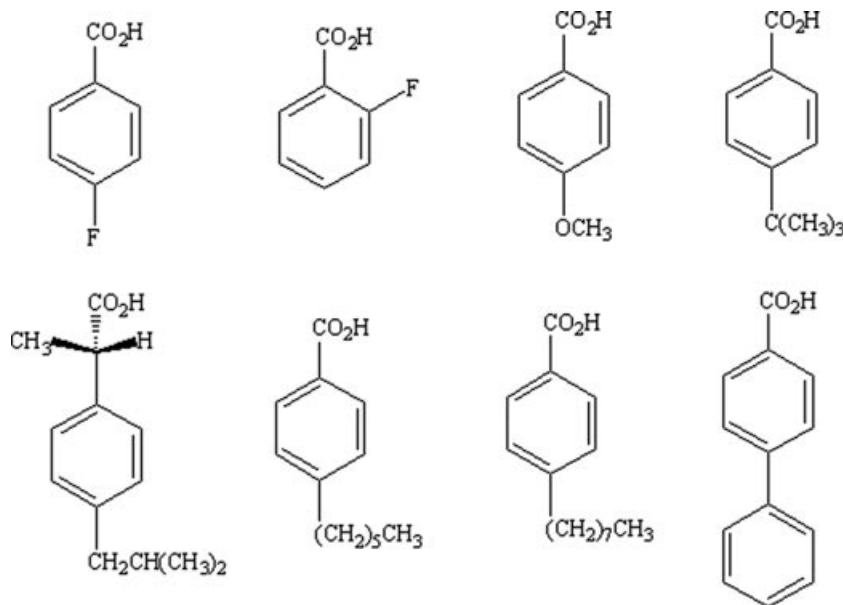


Figure 4. Structures of the compounds used in the flurbiprofen mixtures. From left to right, top to bottom: 4-fluorobenzoic acid, 2-fluorobenzoic acid, 4-methoxybenzoic acid, 4-*t*-butylbenzoic acid, (*S*)-ibuprofen, 4-hexylbenzoic acid, 4-octylbenzoic acid. Biphenyl-4-carboxylic acid was not used as a standard because of the uncertainty associated with the large temperature adjustments. Thermochemical data for 4-isobutylbenzoic acid, another structurally related material, is not currently available.

Table 9. Vaporization Enthalpies of The Solid Standards and (R,S)-Flurbiprofen and at $T = 298.15$ K

Compound	$\Delta H_{\text{sub}}(298 \text{ K})$ kJ mol ⁻¹	$\Delta H_{\text{fus}}(298 \text{ K})$ kJ mol ⁻¹	$\Delta H_{\text{vap}}(298 \text{ K})$ kJ mol ⁻¹
4-Fluorobenzoic acid	93.4 ± 2.4	14.4 ± 2.0	79.0 ± 3.1
2-Fluorobenzoic acid	94.8 ± 0.5	16.3 ± 1.3	78.5 ± 1.4
4-Methoxybenzoic acid	112.5 ± 0.6	21.74 ± 2.4	90.7 ± 2.5
4- <i>t</i> -Butylbenzoic acid	105.2 ± 0.6	10.01 ± 2.4	95.2 ± 2.5
4-Hexylbenzoic acid	122.6 ± 0.8	7.90 ± 1.8	114.7 ± 2.0
Biphenyl-4-carboxylic acid	127.5 ± 4.1	20.0 ± 3.6	107.5 ± 5.5
4-Octylbenzoic acid	140.7 ± 1.6	14.6 ± 2.0	126.1 ± 2.6
(R,S)-Flurbiprofen	110.2 ± 0.5(Ref.6)	21.8 ± 1.8(Ref.6)	88.4 ± 1.9

Table 10. The Correlation of $\Delta H_{\text{vap}}(298 \text{ K})$ with $\Delta H_{\text{trn}}(T_m)$ for Alkanes and 1-Fluoroalkanes

Run 3	Slope [T (K)]	Intercept	$\Delta H_{\text{trn}}(424 \text{ K})$ [kJ mol ⁻¹]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (lit)]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (calcd.)]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (lit)]
Heptane	-2916.7	8.085	24.2	36.6	36.5 ± 0.4	
1-Fluoroheptane	-3471.3	8.727	28.9		42.7 ± 0.4	41.1 ± 0.3
Decane	-4213.9	9.619	35.0	51.4	51.4 ± 0.4	
Dodecane	-5078.0	10.678	42.2	61.5	61.5 ± 0.5	
1-Fluorododecane	-5605.0	11.267	46.6		67.7 ± 0.5	66.9 ± 3.3
Tetradecane	-5942.7	11.745	49.4	71.7	71.7 ± 0.5	
1-Fluorotetradecane	-6459.3	12.312	53.7		77.7 ± 0.5	76.9 ± 4.7

Run 1 (data from Table 2):

$$\Delta H_{\text{vap}}(298 \text{ K})/\text{kJ mol}^{-1} = (1.39 \pm 0.01) \Delta_{\text{trn}}H_m(424 \text{ K}) + (2.67 \pm 0.32) r^2 = 0.9999.$$

Run 2 (Data not included)

$$\Delta H_{\text{vap}}(298 \text{ K})/\text{kJ mol}^{-1} = (1.39 \pm 0.01) \Delta_{\text{trn}}H_m(424 \text{ K}) + (2.68 \pm 0.27) r^2 = 0.9999.$$

As noted in the last two rows of Table 10 and illustrated in Figure 4, the 1-fluoroalkanes are reproduced by the *n*-alkanes, generally within their experimental uncertainty. The success in using these standards in reproducing the vaporization enthalpies of the 1-fluoroalkanes prompted evaluation of the vaporization enthalpy of the flurbiprofens using carboxylic acids and the few fluorocarboxylic acids whose vaporization enthalpies could be evaluated from existing data.

Sublimation enthalpies of the monofluorinated benzoic acids are available and together with their fusion enthalpies, the vaporization enthalpies could

be calculated as indicated above. As their vaporization enthalpies and retention times are very similar, only two of the three were used as standards. This included using the vaporization enthalpies of both the 2- and 4-fluorobenzoic acid along with a variety of other structurally related carboxylic acids. The value recently reported for (S)-ibuprofen¹⁷ was also included, along with the flurbiprofens. The retention times and the resulting correlations for (R,S)-flurbiprofen are summarized in Tables 3 and 11 and in Figure 6.

The same standards were also used in the evaluation of the vaporization enthalpy of the R isomer. The retention times are listed in Table 4 and the results

Table 11. The Correlation of $\Delta H_{\text{vap}}(298 \text{ K})$ with $\Delta H_{\text{trn}}(T_m)$ for Carboxylic Acids and (R,S)-Flurbiprofen

Run 3	Slope [T (K)]	Intercept	$\Delta H_{\text{trn}}(469 \text{ K})$ [kJ mol ⁻¹]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (lit)]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (calcd.)]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (Table 9)]
4-Fluorobenzoic acid	-4789.9	10.867	39.8	78.7	76.9 ± 3.8	
2-Fluorobenzoic acid	-4946.4	10.98	41.1	78.5	79.3 ± 3.8	
4-Methoxybenzoic acid	-5733.8	11.665	47.7	90.7	91.7 ± 4.0	
4- <i>t</i> -Butylbenzoic acid	-6057.6	12.067	50.4	95.2	96.7 ± 4.0	
(S)-Ibuprofen	-6612.2	12.768	55.0	106	105.4 ± 4.3	
Hexylbenzoic acid	-7133	13.324	59.3	114.7	113.5 ± 4.5	
Octylbenzoic acid	-7953.1	14.29	66.1	126.1	126.4 ± 4.8	
(R,S)-Flurbiprofen	-8034.7	14.269	66.8		127.6 ± 4.9	88.4 ± 1.9

Run 3 (Data from Table 3).

$$\Delta H_{\text{vap}}(298 \text{ K})/\text{kJ mol}^{-1} = (1.88 \pm 0.057) \Delta_{\text{trn}}H_m(469 \text{ K}) + (1.95 \pm 3.0) r^2 = 0.9954.$$

Run 4 (Data not included).

$$\Delta H_{\text{vap}}(298 \text{ K})/\text{kJ mol}^{-1} = (1.85 \pm 0.068) \Delta_{\text{trn}}H_m(469 \text{ K}) + (2.65 \pm 3.6) r^2 = 0.9933.$$

Table 12. The Correlation of $\Delta H_{\text{vap}}(298 \text{ K})$ with $\Delta H_{\text{trn}}(T_m)$ for Various Carboxylic Acids and (R)-Flurbiprofen

Run 3	Slope (K)	Intercept	$\Delta H_{\text{trn}}(469 \text{ K})$ [kJ mol ⁻¹]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (lit)]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (calcd.)]	$\Delta H_{\text{vap}}(298 \text{ K})$ [kJ mol ⁻¹ (Table 9)]
4-Fluorobenzoic acid	-4655.8	10.54	38.7	78.7	76.9 ± 3.6	
2-Fluorobenzoic acid	-4809	10.658	40	78.5	79.1 ± 3.7	
4-Methoxybenzoic acid	-5692.2	11.571	47.3	90.7	92.3 ± 3.9	
4- <i>t</i> -Butylbenzoic acid	-5970.8	11.889	49.6	95.2	96.4 ± 4.0	
(S)-Ibuprofen	-6569	12.682	54.6	106	105.3 ± 4.2	
Hexylbenzoic acid	-7126.2	13.319	59.2	114.7	113.6 ± 4.4	
Biphenyl-4-carboxylic acid	-7398.5	13.35	61.5		117.6 ± 4.5	107.5 ± 5.5
Octylbenzoic acid	-7983.1	14.362	66.4	126.1	126.3 ± 4.7	
(R)-Flurbiprofen	-8058.3	14.329	67		127.4 ± 4.7	

Run 5 (Data from Table 4).

$$\Delta H_{\text{vap}}(298 \text{ K})/\text{kJ mol}^{-1} = (1.79 \pm 0.056) \Delta_{\text{trn}}H_m(469 \text{ K}) + (7.64 \pm 2.9) r^2 = 0.9951.$$

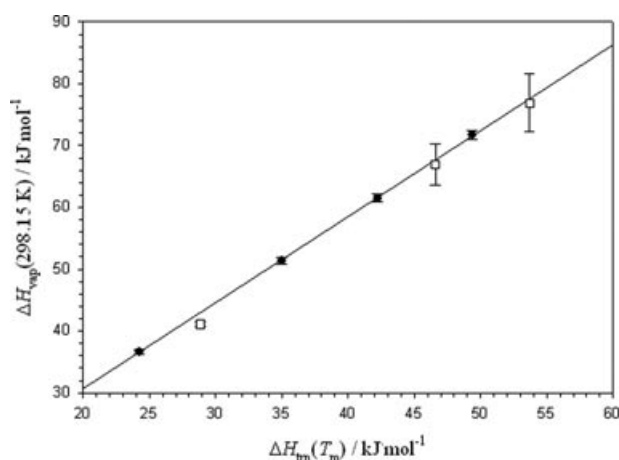


Figure 5. A plot of vaporization enthalpy at $T = 298.15$ K against the enthalpy of transfer measured at a mean temperature of $T = 424$ K, illustrating the correlation between n -alkanes and their 1-fluoro derivatives. Values of $\Delta H_{\text{vap}}(298 \text{ K})$ for the 1-fluoroalkanes (\square) were not used in generating the line calculated by linear regression. Uncertainties are literature values.

are summarized in Table 12. As indicated in Table 12, biphenyl-4-carboxylic acid was also included in this mixture but its vaporization enthalpy was not used in the correlation for the reasons cited above. The resulting vaporization enthalpy obtained by the correlation for this material is basically within the uncertainties estimated.

The vaporization enthalpies of the chiral and racemic forms of a substance are expected to differ but be very similar in magnitude. Examination of the results of Tables 11 and 12 confirm this expectation. Small differences in vaporization enthalpy between enantiomer and racemate have also been observed in other chiral systems as well.^{14,29} Additionally, to determine whether (R,S)- and (R)-flurbiprofen have different retention times, a mixture of the two forms were injected simultaneously at both the lower and upper temperature used in the gas chromatographic analysis. Only a single peak was observed at both temperatures.

DISCUSSION

The results of this work for both flurbiprofens and biphenyl-4-carboxylic acid are summarized in

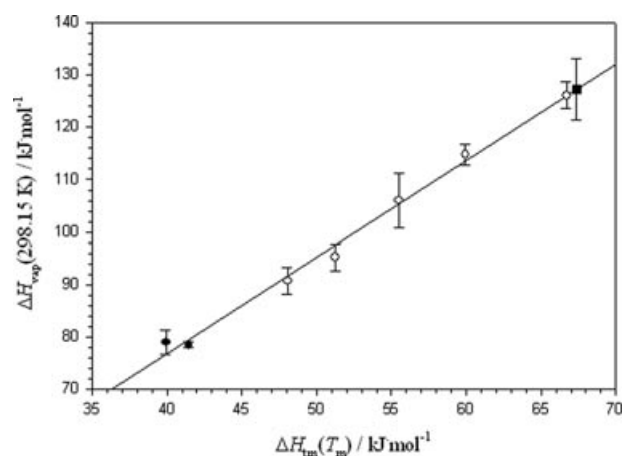


Figure 6. The correlation obtained between $\Delta H_{\text{vap}}(298 \text{ K})$ and $\Delta H_{\text{tm}}(469 \text{ K})$ using both mono-fluorinated (\bullet) and non-fluorinated carboxylic acids (\circ) as standards. The vaporization enthalpy for (R,S)-flurbiprofen (\blacksquare) from the correlation and its uncertainty is also included. The other uncertainties are literature values. The line represents the results of a linear regression analysis of the standards.

Table 13. Included in this table is the fusion enthalpy of (R,S)-flurbiprofen, the total solid–solid and solid–liquid phase transitions from $T = 298.15$ K to T_{fus} for the (R)-enantiomer, the fusion enthalpy measured for biphenyl-4-carboxylic acid, all adjusted to $T = 298.15$ K, their vaporization enthalpies at $T = 298.15$ K, and the resulting sublimation enthalpies calculated using Eq. 1. As indicated in Table 13, the sublimation enthalpy calculated for (R,S)-flurbiprofen of $155.6 \pm 5.8 \text{ kJ mol}^{-1}$ varies substantially from the literature value of $110.2 \pm 0.5 \text{ kJ mol}^{-1}$. We have no explanation for the discrepancy observed. The sublimation enthalpy of (R)-flurbiprofen is evaluated as $145.1 \pm 5.8 \text{ kJ mol}^{-1}$. Despite the fact that the sublimation enthalpies of the chiral and racemic forms are within their uncertainties, the difference in fusion enthalpy, $4.9 \pm 0.4 \text{ kJ mol}^{-1}$, is probably the best indicator of the difference in sublimation enthalpy between the two forms. Finally, according to the results obtained by correlation gas chromatography and DSC, the sublimation enthalpy at $T = 298.15$ K of biphenyl-4-carboxylic acid is predicted to be approximately 10 kJ mol^{-1} larger than the value measured by Calvet drop calorimetry. However, when the

Table 13. Vaporization and Sublimation Enthalpies of Flurbiprofen and Comparison with the Literature^a

	$\Delta H_{\text{vap}}(298 \text{ K})$ (kJ mol ⁻¹)	$\Delta H_{\text{vap}}(298 \text{ K})_{\text{avg}}$	$\Delta H_{\text{fus}}(298 \text{ K})$ (kJ mol ⁻¹)	$\Delta H_{\text{sub}}(298 \text{ K})$ (kJ mol ⁻¹)		
				This work	Lit	Lit
(R,S)-Flurbiprofen	$127.6 \pm 4.9 / 127.3 \pm 5.8$	127.5 ± 5.5	21.8 ± 1.8	149.3 ± 5.8	110.2 ± 0.5	6
(R)-Flurbiprofen		127.4 ± 4.7	17.7 ± 1.7^a	145.1 ± 5.8		TW ^b
Biphenyl-4-carboxylic acid	117.6 ± 4.5	117.6 ± 4.5	20.0 ± 3.6	137.6 ± 5.8	127.5 ± 4.1	10

^aAlso includes the enthalpies associated with the two solid–solid phase transitions observed.

^bThis work.

uncertainties associated with both measurements are taken into consideration, the two numbers are indistinguishable.

ACKNOWLEDGMENTS

Patamaporn Umnahanant would like to thank the Thailand Research Fund MRG5480209, the office of Higher Education Commission, Thailand, and Kasetsart University Research and Development Institute for financial support.

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