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Enthalpy–Entropy Compensation in the Structure-Dependent Effect of Nonsteroidal Anti-inflammatory Drugs on the Aqueous Solubility of Diltiazem

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Certain combinations of acidic and basic drugs can cause significant changes in physicochemical properties through the formation of ionic liquids, eutectic mixtures, or deep eutectic solvents. In particular, combining indomethacin and lidocaine is known to result in apparent increases in both the partition coefficients (hydrophobicity) and aqueous solubilities (hydrophilicity). The physicochemical interactions between drugs change the water solubility of the drugs and affect the bio-availability of active pharmaceutical ingredients. Therefore, we need to clarify the mechanism of changes of water solubility of drugs through the physicochemical interactions. In the present study, we identified a thermodynamic factor that regulates the dissolution of a basic drug, in the presence of various acidic nonsteroidal anti-inflammatory drugs. The results demonstrated that enthalpy–entropy compensation plays a key role in the dissolution of drug mixtures and that relevant thermodynamic conditions should be considered.

Key words solubility; intermolecular interaction; diltiazem; non-steroid anti-inflammatory; entropy; van’t Hoff plot

Introduction

Multidrug combination therapy or polypharmacy is the administration of multiple drugs to a patient. However, there is a possibility that polypharmacy cause side effects and excessive potentiation of drug efficacy. Polypharmacy results from prescription errors and potentially inappropriate medication. Although antipsychotic polypharmacy (APP) and augmentation with other psychotropic drugs are especially common in psychiatric practice, no compelling data justify these strategies. High APP prescribers have more likely a preferred psychiatric practice, no compelling data justify these strategies. In addition, patients with bipolar disorder who are taking antidepressants are at risk of a mania switch, so single-agent administration is not recommended. Since most psychotropic drugs are metabolized by cytochromes and other enzyme systems, drug–drug interactions via drug-metabolizing enzymes or drug-binding proteins have been extensively studied. Current database availability allow lethal polypharmacy to be recognized and provide knowledge about cases in which unfortunate or accidental encounters resulted from unexpected drug combinations allowing pharmacokinetic and pharmacodynamic countermeasures to be achieved. However, further attention should be paid to insufficiently studied physicochemical interactions between inaccurately prescribed drugs.

Physicochemical interactions between drugs change the water solubility of the drugs and affect the bio-availability of active pharmaceutical ingredients. In a recent study, we reported that the weakly acidic drug oxybuprocaine regulates the supersaturation of the acidic drug piroxicam. In another study, we showed that a heat-treated equimolar mixture of indomethacin (IDM) and lidocaine (LDC) transforms into a eutectic mixture, with subsequent cooling forming an amorphous mixture, resulting in enhanced aqueous solubility. This advantageous dissolution behavior is thermodynamically reasonable because pure IDM has a high dissolution enthalpy. Our comparative study on the effects of LDC and other basic drugs on the aqueous solubility of IDM revealed that an equimolar mixture of IDM and LDC exhibits a larger decrease in fusion temperature than mixtures of IDM and other basic drugs. Thus, LDC is considered a highly efficient solubilizer for acidic drugs. Moreover, the decrease in fusion temperature is most prominent for equimolar mixtures of monovalent acidic and basic drugs.

A phase diagram for ibuprofen (IBP; $T_m=329$ K) and LDC at various ratios indicated that the mixtures are peritectic with two phase transition temperatures (293 and 310 K), suggesting the presence of heterogeneous intermediate states at these temperatures. The tendency to form a heterogeneous amorphous phase has been kinetically observed, particularly in IBP-rich mixtures. As illustrated by these examples, the individual behaviors of components are determined by the component with the lower fusion temperature. Thus, the water-soluble amorphous states of IDM/LDC, IBP/LDC, and other mixtures have been investigated because LDC has a lower fusion temperature. Although the hydrochloride salt of LDC ($T_m=347$ K) also exhibits an amorphous state when mixed with IDM, the glass transition occurs at any ratio with-

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out anisotropy.

There is some evidence that acidic and basic drugs form ionic complexes owing to ionic interactions between their dissociated carboxyl groups and protonated ammonium groups, respectively, suggesting that they are not ionic liquids. When the basic drugs cimetidine and famotidine were added to the acidic drugs IDM and diclofenac (DCF), a decrease in solubility was only observed for the combination of DCF and famotidine. An NMR analysis suggested that this phenomenon is due to the formation of an ion pair complex. However, this assignment remains speculative as the NMR spectra of IDM/LDC and IBP/LDC mixtures do not demonstrate obvious proton transfer from carboxyl groups to amines. If and only if a mixture is a typical ionic liquid, its components would be stabilized in an aqueous liquid rather than being dissolved in an aqueous solution. As the solubility of IDM in IDM/LDC mixtures has been observed to be higher than that in neat IDM, the ionic liquid model should be considered for mixtures of weakly acidic and weakly basic drugs.

Although LDC enhances the aqueous solubility of IDM, LDC has recently been shown to suppress the aqueous solubility of IBP. According to the analysis of van’t Hoff’s reaction isobar, the dissolution processes of neat IBP and neat LDC are endothermic and exothermic, respectively. However, the dissolution of an IBP/LDC mixture is an exothermic process. Diffusion-ordered NMR spectroscopy confirmed that IBP and LDC exhibited concerted mobility in a protonic medium but not in aprotic dimethyl sulfoxide-$d_6$. These thermodynamic features and NMR observations suggested that hydrophobic hydration (as an exothermic dissolution process) of LDC in an aqueous environment captured “dehydrated” IBP in the hydrated clathrate surrounding LDC. This behavior differs from hydrophilic complex formation (as an endothermic dissolution process), which facilitates dissolution in a protonic solvent. Thus, an increase in solubility in the presence of phosphate anions could be explained as an effect of the anions, through the bulk phase, on the ionic atmosphere of the drugs. If acidic and basic drugs form a structurally specific complex that improves solubility, a comparison of a series of analogous drugs is expected to reveal the essential moiety for complex formation. However, in a quantitative structure–activity relationship study of analogous local anesthetics, no structural features were identified as having an obvious influence on the water–octanol partition coefficients and aqueous solubility. The only parameters found to affect these properties were the hydrophobicity, the fusion entropy, and the decrease in fusion temperature caused by the formation of a eutectic mixture of local anesthetics with acidic drugs. Thus, it was speculated that the complex is not dissolved in aqueous solution owing to the presence of anion–cation interactions nor is the complex separated from the aqueous phase as an insoluble ionic liquid phase.

The present study aimed to identify the physicochemical requirements for additives that enhance or suppress solubility, assuming that the thermodynamic balance of weakly acidic and weakly basic drugs would regulate their own solubility, namely, the chemical potential for dissolution in solution. Therefore, we compared the effects of weakly acidic drugs—IBP, IDM, aspirin (ASP), ketoprofen (KTP), DCF, and naproxen (NPX)—on the solubility of diltiazem (DTZ), which is a readily available benzodiazepine derivative used as an anti-psychotic drug or mood stabilizer. In addition, as we have frequently used LDC as a representative basic drug, comparisons were made between the behaviors of LDC and DTZ. Conventionally, it has been considered that aqueous solubility and dissolution rate are improved by the formation of an ionic liquid, a eutectic mixture, or a deep eutectic solvent via weakly electrostatic or hydrophilic interactions between drugs. However, the results of this study indicated that the solubility of a mixture can be regulated by the thermodynamic order of the components in the mixture such as entropy.

Experimental

Materials The drugs IBP, ASP, NPX, DCF, and DTZ were purchased from Tokyo Chemical Industry Co. (Tokyo, Japan). The drugs KTP, IDM, and LDC were obtained from Wako Pure Chemical Corporation (Osaka, Japan). All other reagents were of the highest grade commercially available. Salts of the drugs were deionized by trimethylamine addition or by ethyl acetate extraction after the addition of NaOH or HCl, as necessary. Subsequently, the filtrated precipitate was washed with purified water and dried overnight in a desiccator. The obtained free acid or free base was used as a deionized compound.

Dissolution of Neat Acids, Neat Bases, and Mixtures Excess IBP (30 mg), KTP (30 mg), ASP (50 mg), NPX (30 mg), DCF (30 mg), or IDM (30 mg) was melted at 333, 373, 413, 443, 473, or 453 K, respectively, and allowed to cool at 293–300 K. The prepared samples were dissolved in 5 mL of 1/40M phosphate/NaOH buffer solution (pH 6.88), shaken at 120 rpm at 298 K for up to 72 h, and then filtered using a 0.2 μm filter membrane. The concentrations of the filtered samples were measured via HPLC using a reversed-phase InertSustain Swift C18 column (5 μm, 150 × 4.6 mm; GL Sciences Inc., Tokyo, Japan). A column oven (CTO-10AS VP, Shimadzu Corp., Kyoto, Japan) operated at 313 K was used. The samples (10 μL) were injected into an autosampler (SIL-20 A, Shimadzu Corp.), and elution was monitored at wavelengths of 237 nm for DTZ, 264 nm for IBP, 256 nm for KTP, 275 nm for ASP, 330 nm for NPX, 275 nm for DCF, and 320 nm for IDM. The flow rate of 0.5 mL min$^{-1}$ was driven by a pump (LC20-AD, Shimadzu Corp.). A mixed mobile phase (30:70 phosphate buffer (0.0667 M)/methanol) was used with an online degasser (DGU20-A3, Shimadzu Corp.).

NMR Measurements The samples were dissolved in dimethyl sulfoxide-$d_6$ and methanol-$d_4$ at concentrations of more than 16 mM for each component. The NMR spectra of the neat drugs and their mixtures at 303 K were recorded on a 400 MHz spectrometer (JMNEX400, JEOL Ltd., Tokyo, Japan), with the deuterated solvent providing the lock signal. Spectral analyses were performed using Delta NMR processing software version 4.2.0 (JEOL USA Inc., Peabody, MA, U.S.A.). The following parameters were used: gradient amplitude, 0.1–0.3 T m$^{-1}$; spectral width, 4000 Hz; 90° pulse, 6.1 ms; pulsed field gradient width, 2–3 ms; relaxation delay, 15–20 s.

Thermodynamic Parameters for Drug Dissolution To determine the thermodynamic parameters, an excess amount of an acidic drug (30 mg of IBP, 30 mg of IDM, 50 mg of ASP, 30 mg of KTP, 30 mg of DCF, or 30 mg of NPX) was melted at the appropriate temperature. After cooling, each sample was added to 5 mL of 1/40M phosphate/NaOH buffer (pH 6.88) containing 10 mM DTZ or 10 mM LDC. The solutions
were shaken for 72 h at 277, 283, 298, and 363 K in an incubator located in a cold room. Subsequently, the solutions were filtered at the same temperatures. The concentrations of the mixture components were determined using HPLC under the above-described conditions. For each mixture, the apparent enthalpies and entropies of dissolution for the neat acidic drug, the neat basic drug, and both components in mixtures were determined from the slope and intercept on the regression line for a logarithm of concentration–reciprocal temperature plot.

Differential Scanning Calorimetry (DSC) and Entropy of Fusion DSC thermograms were recorded using a DSC 8230 instrument (Rigaku Co., Tokyo, Japan). Samples (10 mg) were placed in a sealed aluminum pan, and measurements were carried out at a scanning speed of 10 K min\(^{-1}\) under nitrogen gas flow (30 mL min\(^{-1}\)). The melting temperature (\(T_m\)) and fusion enthalpy (\(\Delta_{\text{fus}} H\)) were defined as the temperature at which the endothermal signal began and the definite integral of the endothermic peak in the DSC thermogram, respectively. The fusion entropy (\(\Delta_{\text{fus}} S\)) was calculated by dividing \(\Delta_{\text{fus}} H\) by \(T_m\).

Quantum Chemical Calculations The initial crystal structures of the drugs were obtained from the Cambridge Structural Database (CSD; version 5.39). The molecular structures of ASP, IBP, NPX, LDC, KTP, DCF, IDM, and DTZ were extracted from the crystal structures in the CCDC database with identifiers of ACMEBZ,\(^{27}\) COTYOAO,\(^{28}\) ANOMEW,\(^{29}\) LEHQEX,\(^{30}\) KEMRUPE,\(^{31}\) HEGRIX,\(^{32}\) BANMOT,\(^{33}\) and CEFUVJ01,\(^{34}\) respectively. Geometry optimization in single molecules was performed in Gaussian 09 using a temperature of 298.15 K and a pressure of 1 atm. Ab initio calculations with the restricted Hartree–Fock (RHF) self-consistent-field approximation, density functional theory (DFT) calculations with Becke’s three-parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional (B3LYP), and post-Hartree–Fock calculations with the second-order Möller–Plesset perturbation (MP2) were carried out for LCAO molecular orbitals using the Pople-type 6-31 Gaussian function basis set including polarization functions for \(p\)- and \(d\)-orbitals (6-31G(d,p)).\(^{35}\) Subsequently, normal mode analyses were performed using the default procedure in Gaussian 09 to obtain the thermodynamic parameters individually assigned to intramolecular fluctuations.

Results and Discussion Dissolution Behaviors of Mixtures of Acidic Drugs with DTZ To estimate the stoichiometry between weakly acidic drugs (IBP, KTP, ASP, NPX, DCF, and IDM) and DTZ required for dissolution in aqueous solution, we initially examined the concentration of IBP in the presence and absence of DTZ over time. Figure 1a shows the dissolution profiles for IBP concentration in DTZ solutions. The IBP concentrations in the neat IBP sample and the 10 mM DTZ mixture were 19 and 5.9 mM, respectively. The solubility of IBP was reduced 65% in the presence of 10 mM DTZ, which suggested that a specific intermolecular interaction occurs between IBP and DTZ molecules in aqueous solution. According to our previous study, in a medium containing 1/40 M phosphate/NaOH buffer at pH 6.88, the predicted concentration of IBP after 24 h is 13 mM,\(^{36}\) which agrees well with the results of the present study (Fig. 1a). Similar to the IBP dissolution curve, the KTP, ASP, NPX, DCF, and IDM dissolution curves became asymptotic at concentrations of 13, 70, 12, 2, and 1.2 mM, respectively (Figs. 1b–1f).

The solubilities of IBP, KTP, ASP, NPX, DCF, and IDM determined at 72 h decreased in proportion to the concentration of DTZ as an additive (Fig. 2). The solubility of DTZ in the mixtures also decreased. The dotted line in Fig. 2a indicates the initial concentration of DTZ in the medium, and the decrease in the solubility of DTZ seems to correspond to that of
IBP. We determined the solubility decrease for IBP and DTZ occurred at a molar ratio of 4:1 by measuring the decrease in the IBP concentration in the presence and absence of 10 mM DTZ and the decrease in the DTZ concentration from its initial concentration (10 mM). Although a similar trend was observed for the solubilities of KTP and DTZ, the solubility decrease was estimated to occur at a molar ratio of 2:1. Similar behavior was observed for NPX/DTZ, DCF/DTZ, and IDM/DTZ at molar ratios of 2:3, 2:3, and 2:1, respectively. In contrast, the mixture of DTZ and ASP exhibited distinctive behavior, with the initial concentration of DTZ remaining constant regardless of the ASP concentration.

**NMR Spectra of Mixtures of Acidic Drugs with DTZ**

To investigate the interactions between DTZ and IBP, KTP, or ASP as well as the effects of hydrogen bonding, $^1$H- and $^{13}$C-NMR spectra were collected in methanol-$d_4$, a protonic solvent, and in dimethyl sulfoxide-$d_6$, an aprotic solvent. Figure 3 shows the differences in the chemical shifts for equimolar mixtures of DTZ and the acidic drugs. In the $^1$H-NMR spectrum of an equimolar mixture of DTZ and IBP in dimethyl sulfoxide-$d_6$, 15 signals assigned to DTZ (the four geminal protons of the two methylene groups exhibited different chemical shifts) and 7 signals assigned to IBP (no signal was observed for the carboxyl proton) had chemical shifts almost identical to those of neat DTZ and IBP, with virtually no changes in the $^{13}$C-NMR signals (the $^1$H- and $^{13}$C-NMR data are summarized in Supplementary Tables S1–S6). $^1$H-$^1$H-correlation spectroscopy (COSY) NMR spectra of mixture samples are shown in Supplementary Fig. S1, and the $^1$H-NMR data of equimolar mixtures of NSAIDs and DTZ or DTZ HCl are summarized in Supplementary Table S7. For the equimolar mixtures of KTP/DTZ and ASP/DTZ, the signals of the dimethylaminoethyl protons of DTZ shifted to higher magnetic fields. The conformations of these rotatable substituents could be changed by an anisotropic effect induced by an excess of the acidic drug. As $^{13}$C-NMR signals of the carboxyl groups in KTP and ASP also shifted to higher magnetic fields, these carboxyl groups were speculated to interact with the dimethylaminoethyl group of DTZ. In methanol-$d_4$, the differences in the chemical shifts ($\Delta \delta$) were more significant than those in dimethyl sulfoxide-$d_6$. It was suggested that this behavior is related to the interactions between the solvent and the solute, which are affected by the hydrogen bonding factor of the solvent.

**Dissolution Enthalpy of Components in Mixtures of Acidic Drugs with DTZ**

Thermodynamic approaches can be used to explain the self-organization of solutions composed of weakly acidic and weakly basic drugs. The solubilities of IBP in the presence of 10 mM DTZ, neat IBP, and neat DTZ at temperatures of 277, 283, 298, and 310 K were measured at 72 h. Subsequently, the logarithm of concentration–reciprocal temperature plots (van’t Hoff plots; Supplementary Fig. S3a) were built. The dissolution enthalpy, $\Delta_{\text{dis}}H$, and the dissolution entropy, $\Delta_{\text{dis}}S$, were determined from the slope and intercept on the regression line, respectively. The dissolution of neat IBP was an endothermic process, whereas that of neat DTZ was exothermic. However, in the case of the IBP/DTZ mixture, the dissolution of each component was found to be exothermic. These results correspond to those of our previous study regarding the exothermic dissolution of IBP in LDC solution in phosphate/NaOH buffer. Thus, the dissolution behavior of IBP was altered in both the IBP/DTZ and IBP/LDC mixtures.

As shown in Supplementary Figs. S3b and S3c, endothermic dissolution processes were observed for both neat KTP and KTP in the KTP/DTZ mixture as well as neat ASP and ASP in the ASP/DTZ mixture. In addition, for the NPX/DTZ, DCF/DTZ, and IDM/DTZ mixtures, the regression lines for NPX in the NPX/DTZ mixture and DCF in the DCF/DTZ

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**Fig. 2. Effect of DTZ Concentration on NSAID Solubility:** (a) IBP/DTZ, (b) KTP/DTZ, (c) ASP/DTZ, (d) NPX/DTZ, (e) DCF/DTZ, and (f) IDM/DTZ

Closed circles: NSAIDs in mixtures; open circles: DTZ in mixtures. The dotted lines indicate the initial concentration of DTZ in the medium.
mixture corresponded to vertically translated lines for neat NPX and neat DCF, and the slopes of the ASP, NPX, and DCF regression lines did not change. In contrast, the slopes of the regression lines for DTZ became acute owing to the coexistence of the acidic drugs. The changes in the $\Delta \text{dis}H$ values of DTZ in the ASP/DTZ, NPX/DTZ, and DCF/DTZ mixtures were biased toward that of neat DTZ. For the dissolution of KTP and IDM in DTZ solution, a more acute decrease in the slope of the acidic drug corresponding to a more acute increase in the slope of DTZ. Consequently, the IBP/DTZ mixture showed a transition to an exothermic process. Overall, the ASP/DTZ, NPX/DTZ, and DCF/DTZ mixtures only showed an increase in $\Delta \text{dis}H$ of DTZ, whereas for the KTP/DTZ and IDM/DTZ mixtures, $\Delta \text{dis}H$ increased for both the acidic drug and DTZ.

Dissolution Enthalpy of Components in Mixtures of Acidic Drugs with LDC Previously, the dissolution of IBP in a mixture with LDC in 1/10 M phosphate/NaOH buffer (pH 6.8) was found to be exothermic. As shown in Supplementary Fig. S4a, in the present study, the dissolution of LDC was exothermic in 1/40 M phosphate/NaOH buffer (pH 6.88). Under these conditions, the dissolution of IBP was also exothermic without a transition to endothermic dissolution in the presence of LDC. Owing to the mild effect of LDC, characteristic phenomena were observed for the ASP/LDC and IDM/LDC mixtures (Supplementary Figs. S4c and S4f), whereas the dissolution processes of other drugs in LDC solution were only slightly affected, in the order of IBP, KTP, NPX, and DCF (Supplementary Figs. S4a, S4b, S4d, and S4e, respectively). In our previous NMR study on an equimolar mixture of IDM/LDC in dimethyl sulfoxide-$d_6$, the $^{13}$C-NMR chemical shifts of the carboxymethyl group and the ring in IDM with which it interacts changed, as did those of the carbonyl group and methylene bridge in the diethylaminoethanoyl group of LDC. These observations indicate the presence of a polar intermolecular interaction between IDM and LDC in the aprotic solvent.

If this intermolecular interaction in aqueous solution caused a large reduction in the dissolution enthalpy, then the constant $\Delta \text{dis}H$ value of LDC could not be rationally explained. Although the $\Delta \text{dis}H$ value of ASP in ASP/LDC also increased, that of LDC in ASP/LDC showed an insignificant decrease. Similarly, although the NMR analysis of the equimolar mixture of ASP/DTZ revealed an intermolecular interaction in the aprotic solvent, the $\Delta \text{dis}H$ value of ASP only showed a slight dependence on the presence of DTZ in aqueous solution (Supplementary Fig. S3c). The changes in $\Delta \text{dis}H$ for an acidic drug in the presence and absence of DTZ in solution, defined as $\Delta \text{dis}H_{(\text{DTZ})}$, were not correlated with any structural descriptors for the acidic drugs illustrated in Chart 1. Furthermore,
ΔΔH\textsubscript{LDC} similarly defined for LDC, showed no significant relationship with the above-mentioned descriptors. Thus, the covariance analysis provided no insights into the observed dissolution behavior.

The results suggest that the changes in the solubilities of the acidic and basic drugs in mixtures were independent of any structural features. The ΔΔH value of an acidic drug likely does not depend on the strength of the intermolecular interactions in dimethyl sulfoxide-d\textsubscript{6}, but is affected by various factors under aqueous conditions, including the coexistence of counter ions, the concentration of phosphate (or kosmotropic) ions, and pH.

Enthalpy–Entropy Compensation in the Dissolution of Weakly Acidic and Weakly Basic Drugs An equimolar mixture of IDM and LDC forms an amorphous state, which increases the solubility. Thermodynamically, the dissolution enthalpy of IDM was positive or negative depending on the presence of absence of LDC, respectively, whereas it was increased by the coexistence of DTZ in solution. A similar but opposite trend was observed for IBP. Although the NMR results suggested the presence of intermolecular interactions in an equimolar mixture of IDM and LDC, no significant interactions were observed in an equimolar mixture of IBP and DTZ.\textsuperscript{19,24} Therefore, IDM and IBP did not show structurespecific affinity for LDC and DTZ, respectively, corresponding to the changes in solubility. Next, we verified the observed thermodynamic properties of the solutions.

Using the van’t Hoff analysis, we calculated not only ΔΔH\textsubscript{dis} but also ΔΔS\textsubscript{dis} from the regression line.\textsuperscript{24} The entropy change–enthalpy plots are presented in Figs. 4a and 4b. Figure 4a shows a linear correlation between the entropy change and the enthalpy change for the mixtures of acidic drugs and DTZ, with a slope and an intercept of 0.0032 K\textsuperscript{-1} and \textasciitilde41.5 J K\textsuperscript{-1} mol\textsuperscript{-1}, respectively.\textsuperscript{38} Figure 4b shows a linear correlation between the entropy change and the enthalpy change for the mixtures of acidic drugs and LDC, with a slope of 0.0035 K\textsuperscript{-1} and an intercept of \textasciitilde38.1 K\textsuperscript{-1} mol\textsuperscript{-1}. These results suggest that enthalpy–entropy compensation was established between the acidic drugs and DTZ or LDC in water.\textsuperscript{39}

The ΔΔH\textsubscript{dis} values for the dissolution of the acidic drugs in aqueous solution were positive, indicating an endothermic process. According to enthalpy–entropy compensation, a positive ΔΔS\textsubscript{dis} value compensates for the loss of enthalpy. This balance optimizes the solubility of the acidic drugs, as suggested

Chart 1. Chemical Structures and Physicochemical Properties of Acidic and Basic Drugs

Fig. 4. ΔS–ΔH Plots for Mixtures of NSAIDs with (a) DTZ and (b) LDC

Closed circles: neat NSAIDs; open circles: NSAIDs in mixtures; closed triangles: neat DTZ; open triangles: DTZ in NSAIDs/DTZ mixtures; closed diamonds: neat LDC; open circles: NSAID concentrations in mixtures; open diamonds: LDC concentrations in NSAIDs/LDC mixtures.
by the Schröder–Le Chatelier equation. Because DTZ has poor solubility, the $\Delta_{\text{dis}}S$ value of DTZ was decreased preferentially to that of the acidic drugs, thus reducing the observed solubility of DTZ. As LDC is more soluble than DTZ in aqueous solution, the decrease in the $\Delta_{\text{dis}}S$ value of LDC was smaller than that of DTZ under the investigated conditions. Thus, these conditions consistently affected the solubility of the acidic and basic drugs.

However, these trends do not explain why IBP and IDM are especially susceptible to the presence of DTZ or why ASP and IDM are more susceptible than the other drugs to the presence of LDC. It remains possible that mutual molecular recognition, i.e., the formation of a specific complex, occurs in these mixtures.

In many reports, when the solubility of each drug changed in the presence of multiple drugs, the research focused on the change in physical properties due to the formation of complexes between the drugs as the cause of the change in solubility. It is true that the solubility of some drugs can be altered by the formation of ion-pair complexes with very small intermolecular distances, such as the combination of famotidine and diclofenac that we reported in our previous study. However, in our study, we found that the solubility of the drug changes not only due to the formation of complexes by intermolecular interactions but also due to the thermodynamic chemical potentials of the molecules. We believe that this finding provides an important clue to the development of a theory for controlling changes in drug water solubility due to physicochemical interactions associated with multidrug prescribing, and to prevent excessive enhancement of drug efficacy by multidrug therapy.

**DSC Thermograms of Mixtures and Neat Drugs** To estimate the fusion enthalpy ($\Delta_{\text{fus}}H$) of the acidic drugs and their mixtures with DTZ, DSC thermograms were collected for the neat samples and equimolar mixtures of the acidic drugs with DTZ (Fig. 5). Supplementary Table S8 lists the obtained melting temperatures, $\Delta_{\text{fus}}H$ values, and fusion entropy ($\Delta_{\text{fus}}S$) values of the prepared samples. Neat DTZ and neat IBP showed endothermic peaks at 379.9 K ($\Delta_{\text{fus}}H=+25.3 \text{kJ mol}^{-1}$) and 329.1 K ($\Delta_{\text{fus}}H=+15.2 \text{kJ mol}^{-1}$), respectively. In contrast, the equimolar IBP/DTZ mixture showed endothermic peaks at 319.0 and 354.2 K, suggesting a eutectic mixture in different proportions. A single peak at 319.9 K ($\Delta_{\text{fus}}H=+15.7 \text{kJ mol}^{-1}$) was obtained at a IBP/DTZ molar ratio of 2:1 (Fig. 5a).

Neat KTP, an equimolar mixture of KTP and DTZ, and a 2:1 KTP/DTZ mixture showed endothermic peaks at 371.8 K ($\Delta_{\text{fus}}H=+25.3 \text{kJ mol}^{-1}$), at 349.6 and 374.3 K, and at 350.4 K ($\Delta_{\text{fus}}H=+41.4 \text{kJ mol}^{-1}$), respectively (Fig. 5b). For ASP and its equimolar mixture with DTZ, endothermic peaks were observed at 413.0 K ($\Delta_{\text{fus}}H=+25.8 \text{kJ mol}^{-1}$) and 368.4 K ($\Delta_{\text{fus}}H=+15.8 \text{kJ mol}^{-1}$), respectively (Fig. 5c). For NPX ($T_m=435.0$ K, $\Delta_{\text{fus}}H=+27.6 \text{kJ mol}^{-1}$), the 1:2 mixture with DTZ showed an endothermic peak at 371.7 K ($\Delta_{\text{fus}}H=+56.2 \text{kJ mol}^{-1}$) (Fig. 5d). For DCF ($T_m=455.5$ K, $\Delta_{\text{fus}}H=+34.1 \text{kJ mol}^{-1}$) and IDM ($T_m=439.2$ K, $\Delta_{\text{fus}}H=+33.8 \text{kJ mol}^{-1}$), the equimolar mixtures with DTZ showed endothermic peaks at 375.9 K ($\Delta_{\text{fus}}H=+24.9 \text{kJ mol}^{-1}$) and 376.1 K ($\Delta_{\text{fus}}H=+25.1 \text{kJ mol}^{-1}$), respectively (Figs. 5e and 5f). Thus, the mixtures of the latter four acidic drugs (ASP, NPX, DCF, and IDM) with DTZ are considered to correspond to eutectic mixtures.

In a previous study on a series of basic drugs, the presence of LDC was shown to decrease the fusion temperature of IBP, thus quantitatively contributing to the change in the solubility of IBP as a basic additive. However, such a criterion is not
applicable in the present study on a series of acidic drugs, as the decrease induced by addition of IBP was obviously smaller than that induced by the addition of ASP or KTP. Moreover, the apparent inhibition of DTZ solubility was more strongly correlated to the concentration of IBP than to the concentration of ASP or KTP (Figs. 2a–2c).

However, $\Delta_{vib}S$ tends to converge at a representative value in a series of similar compounds, as illustrated by the Richardson rule for spherical symmetric molecules and the Walden rule for general organic chemicals. In the present study, the average $\Delta_{vib}S$ value of the acidic drugs, except IBP, was $+69.1 \text{ JK}^{-1} \text{ mol}^{-1}$. Because IBP possesses axial symmetry, the freedom of rotation is reduced and the experimental $\Delta_{vib}S$ value was $+49.1 \text{ JK}^{-1} \text{ mol}^{-1}$, which differed from those of the other drugs by approximately $3R$ (where $R$ is the gas constant).

In contrast, IDM had the highest $\Delta_{vib}S$ value ($+77.1 \text{ JK}^{-1} \text{ mol}^{-1}$) because a wide variety of interconverting IDM structure can be produced by solid/liquid transformations (or solid/solute transformations). Thus, the characteristics of IBP and IDM seem to be reflected by the liquid and solid states. We conclude that the properties in the solid state and interfacial phenomena were not predominantly observed in the thermodynamic solubility and dissolution kinetics experiments.

**Theoretical Calculations** The RHF, B3LYP, and MP2 calculations using the 6-31G(d,p) basis set in normal mode analysis provided thermodynamic parameters that could be individually assigned to intramolecular fluctuations. The absolute entropy values of the translational (open triangles) and rotational (open squares) motions in isolated drug molecules were determined to be $174–183$ and $131–153 \text{ JK}^{-1} \text{ mol}^{-1}$, respectively, from the theoretically valid linear correlation with the natural logarithms of molecular weight. These entropy values were determined independently of the approximation/optimization methods. The total vibrational entropy values of the isolated drug molecules, which were calculated as the sum of the contributions from all vibrational normal modes, increased exponentially with molecular weight (Fig. 6). For the vibrational normal modes with computed infrared intensities of $>10 \text{ kmol}^{-1}$, which were dependent on the approximation/optimization methods, i.e., B3LYP (closed circles), 28, 33, 38, 40, 44, and 58 frequency modes in the range of 4000–400 cm$^{-1}$ were simulated for ASP, IBP, DCF, KTP, NPX, and IDM, respectively. Because the computed infrared intensity is proportional to the square of the electric dipole moment change in the moiety involved in the vibrational mode, the intramolecular interactions in the solid state can be correlated with dissolution in solution. Therefore, the number of vibrational modes with high IR intensities suggests that IBP contains a small number of polar substituents, which can also be inferred from its chemical formula. In contrast, although the number of hydrophilic substituents in IDM was not significantly different from that in DCF, the number of substituents with high IR intensities in IDM was almost double those in DCF and NPX. Thus, this property seems to distinguish IDM from the other acidic drugs.

As shown in Supplementary Fig. S4a, in 1/40M phosphate buffer containing 10 mM LDC, the slope of the regression line for the solubility of IBP did not change, suggesting an exothermic process. In our previous study, the regression line for the solubility of IBP changed in the presence of both excess LDC and 1/10M phosphate buffer, suggesting a transformation from an endothermic to an exothermic process. In addition, LDC reduced the endothermic requirement for the dissolution of IDM, making it an exothermic process, such that the solubility of IDM in the mixture surpassed that of neat IDM at lower temperatures (Supplementary Fig. S4f). These observations suggest that LDC regulates the solubility of another solute without specific complexation with the solute.

Considering the transition from the polar hydration of IDM to the hydrophobic hydration of IDM, LDC may remove the water molecules interacting with IDM, thus enhancing the kosmotropic effect on the aqueous solvent. This effect alone would be inadequate to affect the solubility of IBP, but a high concentration of phosphate ions could enhance the kosmotropic effect of LDC. We speculate that the difference in the sensitivities of IDM and IBP is caused by the intramolecular interactions of IDM itself. Under kosmotropic conditions, the conformational interconversion of IDM would inhibit intermolecular interactions if the polar substituents were hidden within the internal cavity of IDM. In contrast, if the polar substituents of IBP were exposed, the magnitude of the kosmotropic effect of LDC and the buffer may be sufficient to change the IBP solubility. As the molecular weight of ASP is as low as that of IBP, ASP may not undergo intramolecular interconversion. As ASP contains an adequate number of polar substituents, the hydrophobic domains could be rearranged via the formation of a dimer instead of through intramolecular interconversion. The multiple polar substituents and vibrational modes of ASP could contribute to the formation of self-intermolecular interactions, comparable to those of the carboxyl group of IBP. Therefore, ASP could more easily regulate its own solubility in the presence of LDC.

If we assume that DTZ increased the endothermic requirement for the dissolution of IDM, then the observed solubility of IDM in the mixture should be decreased to less than 1/15 of the endothermic requirement of neat IDM at 298 K (Supplementary Fig. S4f). In fact, DTZ weakens the hydrophilic hydration of IDM. The polar substituents of IDM in LDC solution are completely hidden, resulting in the loss of hydrophilic hydration, whereas the polar substituents of IDM in DTZ solution are not completely inhibited, which decreases
the hydrophilicity. Thus, the apparent solubility of IDM in a mixture with DTZ should be lower than that of neat IDM. However, DTZ does not create the kosmotropic conditions necessary to make the dissolution process exothermic. Therefore, DTZ and IDM likely form insoluble complexes. In contrast, the presence of DTZ had little effect on the solubility of ASP. DTZ would selectively bind to IDM instead of ASP. The dissolution of DTZ is based on hydrophobic hydration in aqueous solution, and the exothermic requirement was promoted by acidic additives, i.e., ASP, NPX, DCF, and IDM. However, the dissolution entropy only compensated for the change in dissolution enthalpy induced by these acidic drugs in the case of DTZ. This difference between DTZ and LDC may be because DTZ can undergo intermolecular interconversion to transform its hydrophilic and hydrophobic nature in response to the ionic environment. Also, as shown in Fig. 6, the intramolecular entropy of ASP is smaller than that of other acidic drugs. From this, it is considered that ASP has less vibration, has only translational and parallel motions, and cannot contribute to enthalpy-entropy compensation due to this small amount of property, so it does not affect the solubility of DTZ as shown in Fig. 2(c). On the other hand, the entropy of NPX shown in Fig. 6 is not very large, but NPX has propionic acid in the molecule and can take various molecular structures, so the entropy of NPX can efficiently compensate for enthalpy-entropy compensation and NPX was able to affect the solubility of DTZ.

**Conclusion**

We found that the solubility of weakly acidic drugs in the presence and absence of weakly basic drugs was regulated by enthalpy–entropy compensation via a thermodynamic analysis of the logarithmic solubility–reciprocal temperature plots. Although this discussion remains speculative, we have identified various chemical factors responsible for the change in solubility in the presence of counter-ion additives. A balance between the dissolution enthalpy and dissolution entropy of the acidic drugs is maintained in the presence and absence of the basic drugs DTZ and LDC. Consequently, the solubility of each acidic or basic drug is optimized to accommodate the dissolution entropy. The dissolution entropy is correlated with the vibrational normal modes of the polar substituents and the hydrophilic portions of the solute molecule. However, the dissolution behaviors of solutes are not always predicted by thermodynamic parameters; therefore, intermolecular interactions specific to the counter ion structure result in a particular good solubility in the case of DTZ and IDM. In some cases, such as the combination of famotidine and diclofenac that we reported in our previous study, the solubility of the drug changes due to the formation of ion-pair complexes with very small intermolecular distances. In such cases where the solubility changes significantly due to the complex formation between coexisting drugs, so it is difficult to predict the change in solubility only from the thermodynamic viewpoint based on chemical potentials.

In this study, we selected NSAIDs as model drug of acidic drugs and found that the solubility of each acidic or basic drug is controlled by enthalpy-entropy compensation. On the other hand, it has been also reported that acidic drugs such as valproic acid improve the solubility of the weakly basic drug erlotinib, which is classified as Class II in the Biopharmaceutics Classification System (BCS), by ion interaction. In this erlotinib study, the change in the solubility of erlotinib is attributed to the interaction between valproic acid and erlotinib, but by applying the enthalpy-entropy compensation in the solubility of acidic and basic drugs found in this study, we think that it will be possible to analyze changes in solubility from a thermodynamic point of view as well as intramolecular interactions.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Supplementary Materials**

This article contains supplementary materials.

**References**

1) Fincke B. G., Miller D. R., Spiro A. 3rd., *J. Gen. Intern. Med.*, 13, 182–185 (1998). https://doi.org/10.1046/j.1525-1497.1998.00053.x.
2) Jyrkkä J., Enlund H., Korhonen M. J., Sulkava R., Hartikainen S., *Drugs Aging.*, 26, 1039–1048 (2009). https://doi.org/10.2165/1131953-00000000-00000.
3) Avery A. J., Ghaleb M., Barber N., Dean Franklin B., Armstrong S. J., Serumaga B., Dhillon S., Ffreyer A., Howard R., Talabi O., Mehta R. L., *Br. J. Gen. Pract.*, 63, e543–e553 (2013). https://doi.org/10.3399/bjgp13X670676.
4) Masnoon N., Shakib S., Kalisch-Ellett L., Caugey G. E., *BMC Geriatr.*, 17, 230 (2017). https://doi.org/10.1186/s12877-017-0642-2.
5) Orenzio S., Jorge O.M.B., *Front Pharmacol.*, 10 302 (2019). https://doi.org/10.3389/fphar.2019.00302.
6) Stahl S., Grady M., *Comparing Monotherapy with Polypharmacy and Augmentation*, *CMAJ.*, 11, 313–327 (2004). https://doi.org/10.2176/929260743456070.
7) Correll C. U., Shaikh L., Gallego J. A., Nachbar J., Olshanskiy V., Kishimoto T., Kane J. M., *Schizophr. Res.*, 131, 58–62 (2011). https://doi.org/10.1016/j.schres.2011.02.016.
8) Suppes T., *Am. J. Psychiatry*, 167, 738–740 (2010).
9) Sandson N. B., Armstrong S. C., Cozza K. L., *Psychosom. Med.*, 46, 463–494 (2005).
10) Burt J., Elmore N., Campbell S. M., Rodgers S., Avery A. J., Payne R. A., *BMC Med.*, 16, 91 (2018). https://doi.org/10.1186/s12876-018-1076-2.
11) Molokhia M., Majeed A., *BMC Fam. Pract.*, 18, 70 (2017). https://doi.org/10.1186/s12875-017-0642-0.
12) Chisaki Y., Aoji S., Yano Y., *Biol. Pharm. Bull.*, 40, 824–829 (2017). https://doi.org/10.1248/bpb.b16-00930.
13) Abe J., Umetsu R., Uranishi H., Suzuki H., Nishibata Y., Kato Y., Ueda N., Sasaoka S., Hatahira H., Motooka Y., Masuta M., Nakamura M., *PLOS ONE*, 12, e0190102 (2017). https://doi.org/10.1371/journal.pone.0190102.
14) Goto S., “Colloid and Interface Science in Pharmaceutical Research and Development,” Chapter 6, ed. by Oshashi H., Makino K., Elsevier, Amsterdam, 2014, pp. 121–129. https://doi.org/10.1016/B978-0-444-62614-1.00006-5.
15) Fujita M., Goto S., Chatani H., Osuka Y., Shimada Y., Terada H., Inoo K., *RSC Adv.*, 10, 1572–1579 (2020). https://doi.org/10.1039/c9ra09923b.
16) Shimada Y., Goto S., Uchiro H., Hirabayashi H., Yamaguchi K., Hirota K., Terada H., *Colloids Surf. B Biointerfaces*, 102, 590–596 (2013). https://doi.org/10.1016/j.colsurfb.2012.08.060.
17) Löbmann K., Lartiren R., Groholland H., Gordon K. C., Strachan C., *Mol. Pharm.*, 8, 1919–1928 (2011). https://doi.org/10.1021/ mp2002973.
18) Shimada Y., Tateuchi R., Chatani H., Goto S., J. Mol. Struct., 1155, 165–170 (2018). https://doi.org/10.1016/j.molstruc.2017.10.101.

19) Katoaka H., Sakaki Y., Komatsu K., Shimada Y., Goto S., J. Pharm. Sci., 106, 3016–3021 (2017). https://doi.org/10.1016/j.xphs.2017.04.010.

20) Bannach G., Arcaro R., Ferroni D. C., Siqueira A. B., Treu-Filho O., Ionashiro M., Schnitzler E., J. Therm. Anal. Calorim., 102, 165–170 (2010). https://doi.org/10.1007/s10973-010-0939-x.

21) Wang H., Gurau G., Shamshina J., Cojocaru O. A., Janikowski J., MacFarlane D. R., Davis J. H., Rogers R. D., Chem. Sci., 5, 3449–3456 (2014). https://doi.org/10.1039/C4SC01036A.

22) Kasai T., Shiono K., Otsuka Y., Shimada Y., Terada H., Komatsu K., Goto S., Int. J. Pharm., 590, 119841 (2020).

23) Tateuchi R., Sagawa N., Shimada Y., Goto S., J. Phys. Chem. B, 119, 9868–9873 (2015). https://doi.org/10.1021/acs.jpcb.5b03984.

24) Chatani H., Goto S., Kataoka H., Fujita M., Otsuka Y., Shimada Y., Terada H., Chem. Phys., 525, 110415 (2019). https://doi.org/10.1016/j.chemphys.2019.110415.

25) Levis K. A., Lane M. E., Corrigan O. I., Int. J. Pharm., 253, 49–59 (2003). https://doi.org/10.1016/S0378-5173(02)00645-2.

26) Wang K., Sun D.-W., Wei Q., Pu H., Lebenson. Wiss. Technol., 96, 66–74 (2018). https://doi.org/10.1016/j.wit.2018.05.017.

27) Chiari G., Fronczek F. R., Davis S. T., Gandour R. D., Acta Crystallogr. B, 37, 1623–1625 (1981). https://doi.org/10.1107/S0567740881006729.

28) Stone K. H., Ladipas S. H., Stephens P. W., J. Appl. Cryst., 42, 385–391 (2009). https://doi.org/10.1107/S0021889809008450.

29) Friščić T., Halasz I., Stobridge F. C., Dinnebier R. E., Stein R., S., Fábián L., CrystEngComm, 13, 3125–3129 (2011). https://doi.org/10.1039/C0CE00894J.

30) Danylyuk O., Butkiewicz H., Coleman A. W., Sawinska K., J. Mol. Struct., 1150, 28–36 (2017). https://doi.org/10.1016/j.molstruc.2017.08.030.

31) Briard P., Rossi J. C., Acta Crystallogr. C, 46, 1036–1038 (1990). https://doi.org/10.1107/S0108270189004968.

32) Lu C., Laws K., Eskandari A., Sutharflingam K., Dalton Trans., 46, 12785–12789 (2017). https://doi.org/10.1039/C7DT02789C.

33) Stowell J.G., Byrn, S.R., Huang K.-S., "CCDC 198476: Experimental Crystal Structure Determination," the Cambridge Crystallographic Data Center, Cambridge, U.K., 2003. https://doi.org/10.5517/CC6NJGT.

34) Kojić-Prodić B., Ružić-Toroš Ž., Sunićj V., Decorte E., Moimais F., Helv. Chim. Acta, 67, 916–926 (1984). https://doi.org/10.1002/hcla.1984067033.

35) Frisch M. J., Trucks G.W., Cheeseman J.R., Scalmani G., Caricato M., Hratchian H.P., Li X., Barone V., Bloino J., Zheng G., Vreven T., Montgomery J.A., Petersson G.A., Seuferia G.E., Schlegel H.B., Nakatsuji H., Izmaylov A.F., Martin R.L., Sonnenberg J.L., Peralta J.E., Heyd J.J., Brothers E., Ogliaro F., Bearpark M., Robb M.A., Mennucci B., Kudin K.N., Staroverov V.N., Kobayashi R., Normand J., Rendell A., Gomperts R., Zakrzewski V.G., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Gaussian 09, n.d.

36) Van Lieshout R. J., MacQueen G. M., Br. J. Psychiatry, 196, 266–273 (2010). https://doi.org/10.1192/bjp.bp.108.057612.

37) Smith L. A., Cornelius V., Warnock A., Liechti M. J., Taylor D., Bipolar Disord., 9, 551–560 (2007). https://doi.org/10.1111/j.1399-5618.2007.00468.x.

38) Dannenfelser R.-M., Yalkowski S. H., Ind. Eng. Chem. Res., 35, 1483–1486 (1996). https://doi.org/10.1021/ie940581z.

39) Gilbert A. S., Thermochim. Acta, 428, 1–9 (2005). https://doi.org/10.1016/j.tca.2004.09.015.

40) Patel K., Doodapenri R., Patki M., Sekag V., Bagde A., Singh M., AAPS PharmSciTech, 20, 135 (2019). https://doi.org/10.1208/s12249-019-1332-0.