Formation of the Racemic Compound of Ephedrine Base from a Physical Mixture of Its Enantiomers in the Solid, Liquid, Solution, or Vapor State

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Received August 20, 1991; accepted February 4, 1992

Physical mixtures (conglomerates) of the two enantiomers of ephedrine base, each containing 0.5% (w/w) of water, were observed to be converted to the 1:1 racemic compound in the solid, liquid, solution, or vapor state. From a geometrically mixed racemic conglomerate of particle size 250–300 μm (50–60 mesh), the formation of the racemic compound follows second-order kinetics (first order with respect to each enantiomer), with a rate constant of 392 mol^{-1} hr^{-1} at 22°C. The reaction appears to proceed via the vapor phase as indicated by the growth of the crystals of the racemic compound between diametrically separated crystals of the two enantiomers in a glass petri dish. The observed kinetics of conversion in the solid state are explained by a homogeneous reaction model via the vapor and/or liquid states. Formation of the racemic compound from the crystals of ephedrine enantiomers in the solution state may explain why Schmidt *et al.* (*Pharm. Res.* 5:391–395, 1988) observed a consistently lower aqueous solubility of the mixture than of the pure enantiomers. The solid phase in equilibrium with the solution at the end of the experiment was found to be the racemic compound, whose melting point and heat of fusion are higher than those of the enantiomers. An association reaction, of measurable rate, between the opposite enantiomers in a binary mixture in the solid, liquid, solution, or vapor state to form the racemic compound may be more common than is generally realized.

KEY WORDS: enantiomers; ephedrine; racemic compound; binary mixture; conglomerate; heat of fusion; thermodynamics; solubility; differential scanning calorimetry; solid–solid reactions.

INTRODUCTION

The importance of chiral drugs has increased the awareness of pharmaceutical scientists of the physical properties of their binary mixtures (1), particularly solubility (2–5). Attempts have been made to relate the interactions on mixing, expressed by the changes in free energy, to the fundamental thermodynamic properties of the enantiomers. The prediction of solute–solvent interactions from various fundamental physical properties (6) have suggested that ephedrine solute–solute stereoisomeric interactions, which give rise to solubility differences, may also be predicted from fundamental thermodynamic properties (4). These considerations led Schmidt *et al.* (4) to apply thermodynamic principles to the prediction of the solubilities of binary mixtures of the enantiomers of ephedrine. These authors stated, "Interestingly the total solubility of ephedrine and pseudoephedrine in binary mixture is consistently lower than that of (1R:2S)-ephedrine alone."

This report is an attempt to explain the lower solubility of the binary mixture compared to the individual enantiomers of ephedrine. We demonstrate that the lower solubility observed by Schmidt *et al.* (1988) can be explained by the formation of a 1:1 racemic compound (a crystalline addition compound containing an equal number of molecules of each of the two enantiomers of ephedrine) from a physical mixture of its enantiomers in the solution state. We also report the formation of the racemic compound from a physical mixture of the opposite enantiomers in the solid, liquid, or vapor states; the kinetics of this conversion in the solid state are found to be of the second order overall (i.e., first order with respect to each enantiomer). A homogeneous reaction model via the vapor and/or liquid states is developed to explain the observed second-order kinetics. The thermodynamics of this reaction are evaluated from the fusion data determined by differential scanning calorimetry. Further, the use and limitations of differential scanning calorimetry to monitor the reaction between the enantiomers in the solid state are discussed.

MATERIALS AND METHODS

Materials

(*RS*)-Ephedrine and (*SR*)-ephedrine hemihydrate and racemic ephedrine hydrochloride were obtained from Sigma Chemical Company (St. Louis, MO). Both the enantiomers were stored under reduced pressure over anhydrous calcium sulfate (Drierite) for 72 hr before use. After drying both the enantiomers were found to contain approximately 0.5% (w/w) of water. Hereafter, (*RS*)- and (*SR*)-ephedrines are referred to as *l*- and *d*-ephedrine, respectively. Racemic ephedrine base (*dl*-ephedrine) was prepared from an aqueous solution of its hydrochloride salt by adding equimolar sodium hydroxide.

Methods

Differential Scanning Calorimetry (DSC)

The DSC curves were recorded on a DuPont Model 910 instrument equipped with a data station (Thermal Analyst 2000, DuPont Instruments, Wilmington, DE). The cell constant was determined and the temperature axis was calibrated using indium (10 mg, 99.99% pure, 28.4-J/g heat of fusion, and peak maximum at 156.6°C). Samples (3 to 5 mg) in crimped aluminum pans were heated at a rate of 10°C/min under nitrogen purge.

X-Ray Powder Diffractometry

The powder X-ray diffraction patterns of the samples were determined using a Rigaku Model 2011 diffractometer. Samples in aluminium holders were scanned at 2θ values between 5 and 35° at a rate of 1° 2θ/min.

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0724-8741/92/0800-1083$06.50/0

Solid-State Kinetics

To 100 mg of *l*-ephedrine in a glass vial (5-ml capacity), 100 mg of *d*-ephedrine was added in five portions of 20 mg each. After each addition, the two solids were mixed with a spatula. The contents of each vial were mixed within 3 min. Thirty-three such mixtures, each in a separate vial, were prepared. The vials were closed tightly with a screw cap and stored at ambient temperature (22 ± 1°C) in a desiccator. After a defined time period had elapsed, one vial was opened, the contents were mixed, 3 to 5 mg of the sample was quickly taken, and the DSC curve of the sample was recorded. The time taken for sampling, weighing, and the start of the DSC run was 1.5 to 2 min. The measurement made immediately after the mixing process was taken as the measurement at time zero. For each time point, the time between the "end of mixing" and the "sampling" was taken as the kinetic time. The time of mixing and the time taken for the DSC curve to be recorded were measured in minutes and were very small compared to the duration of the kinetic experiments, which were measured in hours. Each vial was used for one measurement and the remaining contents were discarded. The experiments were so designed that three such vials were analyzed at each of 11 time points.

Conversion in the Solution State

Each of the enantiomers (500 mg) was added to 8 ml of distilled water in a glass vial (20-ml capacity) which was maintained at 30 ± 1°C for 72 hr. After 72 hr, 2 ml of the slurry were quickly filtered and dried over anhydrous calcium sulfate (Drierite) for 15 min. The X-ray powder diffraction pattern and DSC curve of the solid phase were recorded.

Conversion in the Liquid State

Each of the enantiomers (200 mg) was weighed into a vial (5 ml) maintained at 50°C. The molten liquid mixture solidified after cooling to room temperature over a period of 2 hr. The X-ray powder diffraction pattern and DSC curve of the solid phase were recorded.

Conversion in the Vapor State

The enantiomers (500 mg of each) were placed diametrically opposite to each other in a glass petri dish. The lid was closed tightly using cellulose adhesive tape (3M Company, St. Paul, MN). Crystals which grew at the center of the petri dish were analyzed using X-ray powder diffraction and DSC.

Construction of the Phase Diagram of Ephedrine Enantiomers

Fused mixtures of various compositions of the pure enantiomers were maintained at −20°C in a freezer for 2 weeks. The mixtures were annealed by keeping them in a desiccator at 22°C for 48 hr and their DSC curves were then recorded.

Estimation of the Kinetic Parameters

The regression parameters of the second-order reaction model were estimated using the ADAPT programs (7,8). The variances of the observations at each time point were judged to be the same and equal weighting was used in parameter estimation.

RESULTS AND DISCUSSION

Vapor-State Reaction

As shown in Fig. 1, the needle-shaped crystals were found to grow in the center of the glass petri dish when the crystals of the two enantiomers were kept diametrically separated. These needle-shaped crystals have the same X-ray powder diffraction pattern and DSC curve (melting point, 77°C) as *dl*-ephedrine. Thus, the crystalline product formed is the racemic compound of ephedrine. These crystals became visible to the naked eye after 16 to 24 hr. This reaction suggests that the enantiomers of ephedrine have a sufficiently high vapor pressure to enable them to react in the vapor state to form the racemic compound. Crystals of the racemic compound were also found to grow on the crystals of the enantiomers.

Phase Equilibrium Diagram of Ephedrine Enantiomers

The individual enantiomers of ephedrine are hygroscopic. Exposure to atmospheric moisture, even during weighing, was found to alter the melting point significantly (by 2 or 3°C). It was therefore necessary to protect the samples from the atmosphere or reduce the time of exposure to a minimum. This observation may explain why the phase

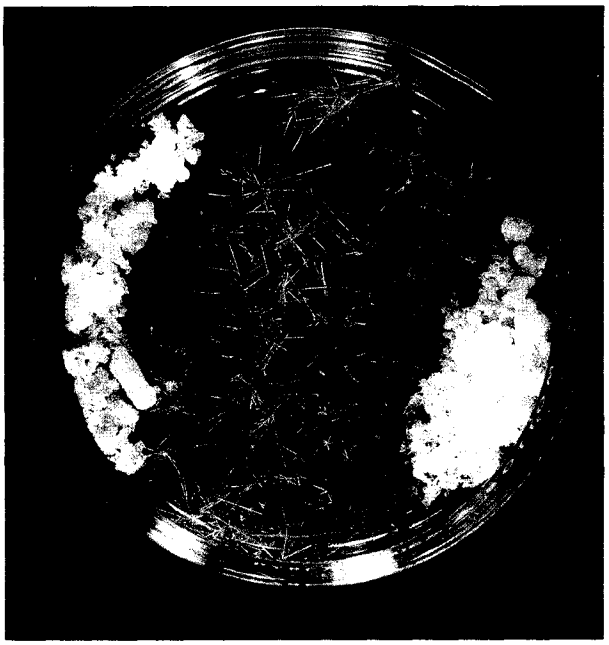

Fig. 1. Photograph showing the growth of the racemic compound of ephedrine, consisting of needles at the center of a glass petri dish, from vapors of the individual enantiomers kept diametrically separated. The crystals on the left are of *l*-ephedrine; those on the right are of *d*-ephedrine.

equilibrium diagram of ephedrine enantiomers has not been recorded previously. However, after exposure to atmospheric moisture, no significant change in the heat of fusion was observed.

To demonstrate the existence of the racemic compound, the phase equilibrium diagram of the ephedrine enantiomers was constructed using DSC. The racemic compound, which appears to dominate Fig. 2, has a heat of fusion (5.82 kcal/mol) and a melting point (77°C) which are appreciably higher than those of the enantiomers (3.54 kcal/mol and 34°C, respectively). The measured melting points (T^f) are significantly lower, by 1 or 2°C, than those predicted theoretically by the Prigogine–Defay equation (9) (Appendix). The trace quantity of water (0.5%, w/w) in each enantiomer may be responsible for these slightly reduced melting points.

The crystals of the racemic compound are long and needle-shaped. The eutectic temperature (32°C), which was found to vary slightly, is very close to the melting point of the enantiomers (34°C). Figure 3 shows a plot of $\ln x(1 - x)$ against $1/T^f$; the estimated ΔH^f_r value from the slope (5.87 kcal mol^{-1}) was found to be in good agreement with the value measured directly by DSC (5.82 kcal mol^{-1}), indicating close agreement between the experimental data and the Prigogine–Defay equation (Appendix) despite the trace quantity of water (0.5%, w/w) in each enantiomer.

As recommended by Jacques *et al.* (10), we use the term "racemic compound" to designate the crystalline addition compound (such as racemic ephedrine) in which the two enantiomers are present in equal quantities within the same crystal lattice. The term "racemic conglomerate" refers to a physical mixture or mechanical mixture of the crystals of individual enantiomers. We refrain from using the terms "racemic mixture" and "true racemate," as they are subject to confusion. Jacques *et al.* (10) recommended that an equimolar mixture of two enantiomers whose physical state is unspecified or unknown be termed a "racemate."

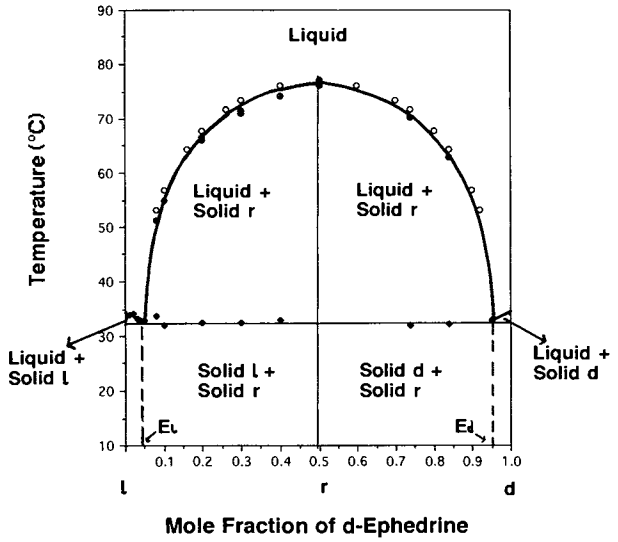

Fig. 2. Phase equilibrium diagram of ephedrine enantiomers. Fill circles are experimentally measured temperatures of complete melting (T^f) and filled diamonds are the experimentally measured temperatures of the first melting, i.e., eutectic temperatures. Open circles are values predicted by Prigogine–Defay Eq. (1) (Appendix). E_l is the eutectic composition between *l*-ephedrine and the racemic ephedrine (*r*), and E_d is the eutectic composition between *d*-ephedrine and racemic ephedrine.

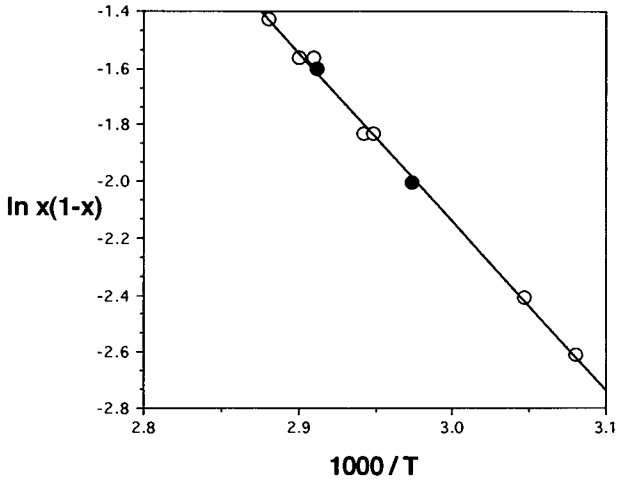

Fig. 3. Test of Prigogine–Defay Eq. (1) (Appendix) for the ephedrine system. Plot of $ln\ x(1 - x)$ versus the reciprocal of the measured values of complete melting (T^f). The open and filled circles, respectively, are the measured T^f values in the left and right halves of Fig. 2.

Liquid-State Reaction

The formation of the racemic compound in the liquid state was found not to be instantaneous. Long and needle-shaped crystals of the racemic compound were found to grow as the mixture was cooled to room temperature. The formation of the racemic compound was found to be practically complete in 2 hr. The solid phase had the same X-ray powder diffraction pattern and DSC curve (melting point, 77°C) as *dl*-ephedrine. Thus, the product formed is the racemic compound of ephedrine.

Solution-State Reaction

The solid phase in equilibrium with the solution at the end of the solubility measurement of an equimolar mixture of the enantiomers was composed of needles, whereas the starting materials (enantiomers) were prism-shaped. The needle-shaped crystals have the same X-ray powder diffraction pattern and DSC curve (melting point, 77°C) as *dl*-ephedrine. Thus, the crystalline product formed is the racemic compound of ephedrine.

The observation by Schmidt *et al.* (4) that the binary mixture of ephedrine enantiomers has a lower solubility than the pure enantiomers can now be attributed to the formation of the racemic compound.

Solid-State Reaction

The rate of formation of the racemic compound from the two enantiomers in the solid state was measurable over many hours. Initial mixing of the opposite enantiomers in the solid state led to a sticky mass. After 2–3 hr, fine, narrow, needle-shaped crystals, characteristic of the racemic compound, appeared on the solid mass. Crystals of the opposite

enantiomers, when placed in contact, were found to liquify partially as observed under a microscope. This observation may explain the viscous nature of the mixture.

The products formed from the solid-, liquid-, solution-, or vapor-state reactions have identical X-ray powder diffraction patterns and DSC curves. This result suggests that, under the experimental conditions mentioned, the same solid phase of the racemic compound arises whether formed from the solid-, liquid-, solution-, or vapor-state reactions. Thus, the racemic compound did not exhibit polymorphism.

Use of DSC for Monitoring the Kinetics of Formation of the Racemic Compound in the Solid State

The dashed lines in Fig. 4 show the phase diagram of the unstable racemic conglomerate, i.e., a physical mixture of the two enantiomers. When such an equimolar physical mixture of two enantiomers is heated, the first endotherm observed in DSC is the melting of the eutectic (i.e., peak A in Fig. 4). The melting of the eutectic is followed by an exotherm (i.e., peak B in Fig. 4) corresponding to the crystallization of the molten eutectic mixture to give the racemic compound. This is followed by a second endotherm which corresponds to the melting of the racemic compound (i.e., peak C in Fig. 4).

When the two enantiomers interact in the solid state to give a racemic compound, the amount of the eutectic remaining (i.e., the area under peak A) decreases with time. After a sufficient period of time the equimolar mixture of the two enantiomers is converted into a single solid phase, the racemic compound. In other words, the system represented by the dashed lines in Fig. 4 is metastable and actually progresses with time toward the equilibrium. After equilibrium has been reached, the DSC curve of the equimolar mixture of the enantiomers has only one endotherm, corresponding to the melting of the racemic compound.

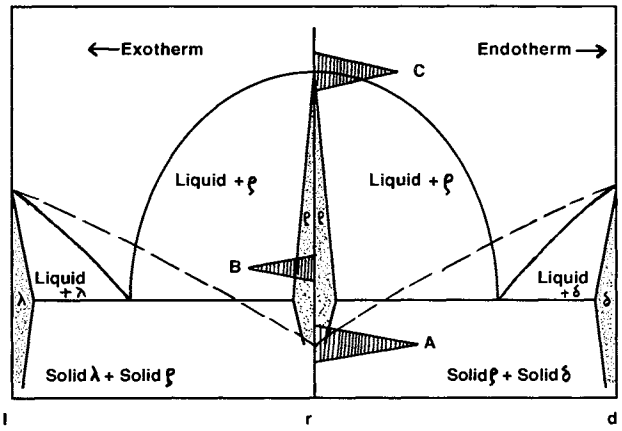

Fig. 4. Schematic diagram showing the sequence of thermal events during heating of a 1:1 solid binary mixture of enantiomers (*l* and *d*) which form a racemic compound (*r*). A, B, and C are the thermal events discussed under Results and Discussion. λ and δ, respectively, are the two terminal hypothetical solid solutions with the enantiomers *l* and *d* in slight excess. ρ is a hypothetical solid solution consisting of the racemic compound with a slight excess of either *l* or *d*. The simple eutectic, metastable equilibrium diagram between *l* and *d* is represented by dashed lines and disappears as $d + l \rightarrow r$. Peaks A and B disappear after a sufficiently long interval of time when solid *l* and solid *d* have been completely converted into *r*, which then melts to give the endotherm C alone. The existence and position of peak B (between A and C) depend on kinetic factors. The areas represented by solid solutions in the diagram have been exaggerated for the purpose of clarity and may not truly represent the actual zones of miscibility.

The heat of transition at the melting point of the eutectic (area under peak A in Fig. 4) in a DSC curve gives a quantitative measure of the sum of the unreacted crystals of the individual enantiomers at any time. Since the heat of fusion of the enantiomers is the same, one-half of the area under peak A in Fig. 4 gives a measure of the unreacted crystals of either one of the enantiomers. From a knowledge of the heat of fusion and initial number of moles of the pure enantiomers, the number of moles of either of the unreacted enantiomers remaining at any time can be calculated.

A small approximation is implicit in the last paragraph, since the heat of fusion of the racemic conglomerate is always lower than that of the pure enantiomer by an amount, $(C^l - C^s) \cdot (T^f_e - T^f_{cong})$, where C^s and C^l are the heat capacities of the solid enantiomer and the racemic liquid, and T^f_e and T^f_{cong} are the melting temperatures of the pure enantiomer and the conglomerate, respectively. Because $(C^l - C^s)$ is typically within the range 20–40 cal mol^{-1} K^{-1} for many organic compounds (10), while the difference in the melting points $(T^f_e - T^f_{cong})$ is about 2 K in the present study, the term, $(C^l - C^s) \cdot (T^f_e - T^f_{cong}) = 60$ cal mol^{-1} for ephedrine, is insignificant compared to the heat of fusion of the pure enantiomers (3.54 kcal mol^{-1}). Hence the heat of fusion of the racemic conglomerate is indistinguishable from that of the pure enantiomers of ephedrine.

During the DSC scan the area under peak B in Fig. 4 decreases with time as the conversion of the enantiomers into the racemic compound progresses. If the crystallization of the racemic compound from the eutectic melt is rapid, the area under peak C in Fig. 4 remains constant with time. In this case, the area under the peak C is not useful in monitoring the kinetics of conversion of the enantiomers into the racemic compound. It is also possible that the racemic compound may not crystallize completely from the eutectic melt before the temperature reaches the melting point of the racemic compound. Even in this case, where the area under the peak C in Fig. 4 increases with time, as the conversion proceeds, the kinetics of the conversion cannot be monitored by measuring the area under peak C in Fig. 4. This is because some of the eutectic melt may react to give the solid racemic compound, which will contribute to the observed heat of fusion, resulting in an overestimation of the racemic compound.

Kinetics of the Solid-State Reaction

Figure 5 shows the representative DSC curves of the physical mixtures over a period of 48 hr after mixing. The number of moles of either of the enantiomers remaining, calculated from the area under the first endotherm in the DSC curve, was plotted against time in Fig. 6. The area under the first endotherm gives a measure of the sum of the number of moles of the two enantiomers present in the mixture at any time. The number of moles of each of the enantiomers present was calculated, indirectly, by dividing the

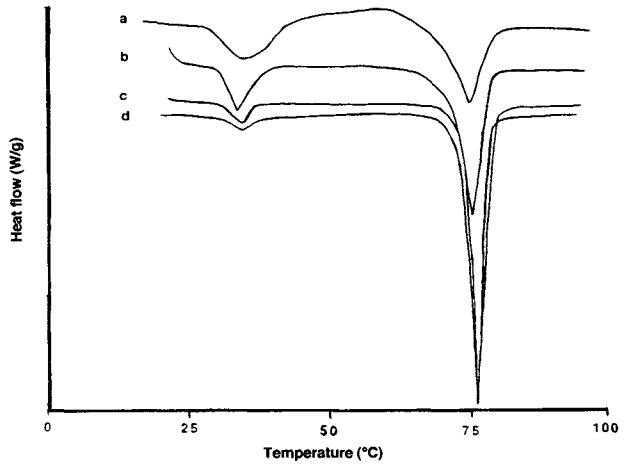

Fig. 5. DSC curves of solid binary mixtures of ephedrine enantiomers showing a decrease in area under the melting endotherm of the eutectic mixture (32°C): (a) 0 hr, (b) 6 hr, (c) 24 hr, and (d) 48 hr.

total number of moles by two. The data were found to fit second-order kinetics with a rate constant $k = 392$ mol^{-1} hr^{-1} ($r^2 = 0.989$) and the solid line in Fig. 6 represents the best-fit line.

The reaction, overall, follows second-order kinetics, meaning that it is of the first order with respect to each of the enantiomers. According to the design of the present experiment, the concentrations of both the enantiomers vary equally, and hence the observed kinetics follow second order. Therefore, not only is the rate of disappearance of both the enantiomers the same, but also it is equal to the rate of formation of the racemic compound. Figure 7 shows the mean values of the number of moles plotted according to the first-, second-, and third-order kinetic models and also according to the model proposed by Rastogi *et al.* (13,14) (Appendix). In plotting the data according to Eq. (6) (Appendix), the number of moles of the racemic compound formed was taken to be equivalent to the thickness of the product layer formed in the original equation.

The data fit the second-order kinetic model better than the other models. The formation of the racemic compound in the vapor state suggests that the solid enantiomers have a sufficiently high vapor pressure that the solid-state conversion may take place via the vapor state. This phenomenon readily explains the observed second-order kinetics (Appendix).

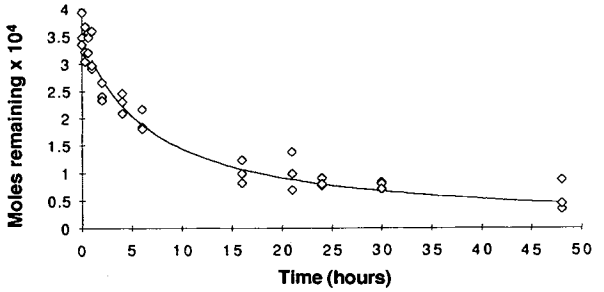

Fig. 6. Plot of the number of moles of either *l*- or *d*-ephedrine remaining versus time. The solid line represents the best-fit line for a second-order plot. The open diamonds represent the actual measurements.

When the two enantiomers of ephedrine, in the solid state, are mixed, some of the mixture is converted into the liquid, and initially, conversion of the enantiomers into the racemic compound also takes place via the liquid state. Since the method involving DSC cannot measure the enantiomers in the liquid state, the rate of conversion in the liquid state cannot be measured using DSC. The conversion in the liquid state may not affect the observed kinetics because the liquid is formed only during initial mixing and the DSC technique monitors the number of moles of the enantiomers only in the solid state. In other words, the design of the reaction is such that only solid–solid, solid–vapor, and vapor–vapor interactions dominate during the kinetic study. According to the current literature, a reaction is termed a "solid-state reaction" if the starting materials are solids, even though mechanistically it may proceed via a vapor or liquid state (e.g., Ref. 12).

Interestingly, the value of n in Eq. (6) (Appendix) obtained from the slope of Fig. 7d is 0.57 and is within the range (0.26–0.59) of the values of n reported for a variety of solid–solid reactions (13,14). Although the data fit a second-order reaction model, the actual mechanism may be a combination of different mechanisms operating simultaneously. The trace quantity of water present in the sample may possibly influence the mechanism and kinetics of the reaction between the enantiomers. Therefore, the observed value of the second-order rate constant may be true only for ephedrine enantiomers containing approximately 0.5% (w/w) of water. As pointed out by Byrn (11), the factors controlling solid–solid reactions and the course of these reactions are yet to be studied in detail. On the other hand, in some complex situations (15), the reaction mechanisms are unknown and their kinetic data cannot be fitted to existing mechanistic models.

Thermodynamics of the Solid-State Reaction

The Gibbs free energy of transfer calculated from Eq. (5) (Appendix) is −1.14 kcal/mol. The typical values for other organic compounds range from 0 to −2.1 kcal/mol (10). The free energy of conversion of the enantiomers of ephedrine into the racemic compound lies between these two extremes. The spectacular conversion observed, even with a free energy value of −1.14 kcal/mol, suggests that this type of conversion may be more common than is generally realized. From Eqs. (2) and (3) (Appendix), the ΔH and ΔS values for the formation of the racemic compound are −2.28 kcal/mol and −3.73 cal/mol K, respectively, neglecting the small heat capacity terms. These results indicate that the process is entropically unfavorable and is driven by the negative enthalpy change.

CONCLUSIONS

The lower solubility observed by Schmidt *et al.* (4) for a binary mixture of ephedrine enantiomers compared to the pure enantiomers may be due to the formation of the racemic compound of ephedrine from its enantiomers in the solution state. Differential scanning calorimetry was found to be a useful technique for monitoring the kinetics of the reaction between the two enantiomers of ephedrine in the solid state.

The kinetics of the reaction in the solid state and the reaction in the vapor state suggest that for solids with an

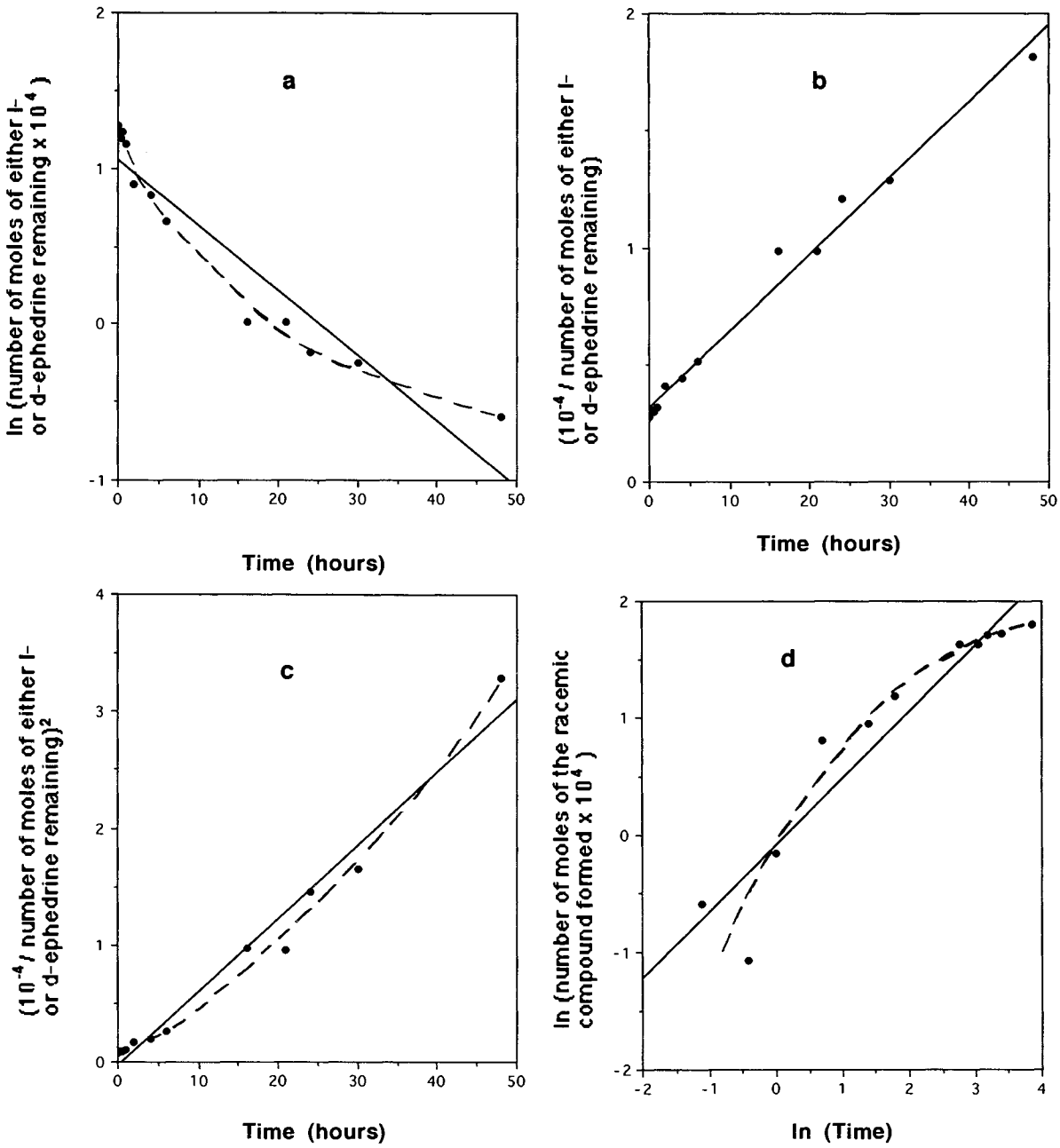

Fig. 7. Plot of the data of the kinetic study according to (a) the first-order reaction model (r^2 = 0.899), (b) the second-order reaction model (r^2 = 0.989), (c) the third-order reaction model (r^2 = 0.973), and (d) Eq. (6) (r^2 = 0.896). The linear regression lines are solid, whereas the dashed curves represent the trend of the experimental measurements.

appreciably high vapor pressure, homogeneous reaction in vapor state may be a major mechanism by which two solids may react. The nature of interactions in the solid and the vapor state shown here may provide further insight into the mechanism of cocrystallization by grinding, in the solid state, which is becoming increasingly useful in the area of organic solid-state chemistry (16). This type of study with enantiomers may have important implications for the handling of the pure enantiomers after resolution and also for studying and understanding the interaction of the enantiomers and their binary mixtures in various states.

APPENDIX

The Applicability of Prigogine–Defay Equation for the Ephedrine System

Prigogine and Defay (9) have developed the following equation, which should apply for all binary systems, including the racemic compounds.

$$\ln 4x(1 - x) = \frac{2\,\Delta H^{f}_{r}}{R}(1/T^{f}_{r} - 1/T^{f}) \qquad (1)$$

where x represents the mole fraction of one of the enantio-

mers in the mixture whose melting point (end of fusion) is T^f (degrees K), T^f_r (also degrees K) and ΔH^f_r (cal mol^{-1}) are the melting point and the heat of fusion of the racemic compound, respectively, and R (1.987 cal mol^{-1}) is the gas constant. From a knowledge of the ΔH^f_r value, the T^f values can be calculated from Eq. (1). Furthermore, by plotting $\ln x(1 - x)$ against the reciprocals of the measured values of T^f, the ΔH^f_r value can be calculated from the slope.

Free Energy, Enthalpy, and Entropy of Formation of the Racemic Compound

These quantities can be calculated from the heats of fusion and melting points of the enantiomers and of the racemic compound at the melting point of the enantiomers (10). The enthalpy of formation of the racemic compound from its enantiomers, at their melting point, is given by Eq. (2),

$$\Delta H_T{}^f_e = \Delta H^f_e - \Delta H^f_r + (C^l - C^s_r) \cdot (T^f_r - T^f_e) \quad (2)$$

where $\Delta H_T{}^f_e$ is the enthalpy of formation of the racemic compound from its opposite enantiomers and ΔH^f_e and ΔH^f_r are the enthalpies of fusion of the enantiomer and of the racemic compound, respectively. C^l and C^s_r are the heat capacities of the liquid and the solid racemic compound and T^f_r and T^f_e are the melting points of the racemic compound and the enantiomer, respectively. The corresponding entropy of formation is given by Eq. (3),

$$\Delta S_T{}^f_e = \Delta S^f_e - \Delta S^f_r + R \cdot \ln 2 + (C^l - C^s_r) \cdot \ln(T^f_r/T^f_e) \quad (3)$$

where $\Delta S_T{}^f_e$ is the entropy of formation of the racemic compound from its opposite enantiomers and ΔS^f_e and ΔS^f_r are the entropies of fusion of the pure enantiomer and of the racemic compound, respectively. The standard thermodynamic relation among free energy, enthalpy, and entropy is given by Eq. (4),

$$\Delta G_T{}^f_e = \Delta H_T{}^f_e - T^f_e \cdot \Delta S_T{}^f_e \quad (4)$$

where $\Delta G_T{}^f_e$ is the Gibbs free energy of formation of the racemic compound from the enantiomers at their melting point. The terms involving heat capacity in Eqs. (2) and (3) can be neglected to a good approximation. Therefore, the free energy of formation of the racemic compound is given by Eq. (5),

$$\Delta G_T{}^f_e = \Delta S^f_r \cdot (T^f_e - T^f_r) - T^f_e \cdot R \cdot \ln 2 \quad (5)$$

Mechanisms of Solid–Solid Reactions

Homogeneous and Heterogeneous Reactions

Reactions between two solids have not been studied extensively. These reactions would not necessarily follow the kinetic models reported in literature for the solid-state decomposition (11,12) since the decomposition reactions are initiated in a single solid phase. Even in solid–solid reactions, the actual mechanism may be heterogeneous (such as vapor–solid, liquid–solid, solid–solid) or homogeneous (such as in the vapor or liquid states).

Heterogeneous Reactions. Rastogi *et al.* (13,14) proposed the following heterogeneous mechanisms for solid–solid reactions: (a) surface migration of one or both reactants, (b) diffusion of one reactant into the grains and channels of the other reactant, and (c) penetration of one reactant into the crystal lattice of the other. By studying the movement of the reaction zone created by the formation of a colored product when the two reactants were placed in capillary tubes, Rastogi *et al.* (13,14) found that when the powders were in contact, the data fitted the following equation:

$$\text{Thickness of the product layer} = kt^n \quad (6)$$

where k is the rate constant, t is the time, and n is a constant. In this case, the plot of the logarithm of the thickness of the product layer against the logarithm of time is linear. When the powders were not in contact, the rate of the reaction decreased and the data fitted the equation

$$\text{Thickness of the product layer} = kt \quad (7)$$

From the activation energies associated with the above reactions, the authors concluded that, when powders are in contact, the mechanism is not vapor diffusion and that intimate contact of the powders allows surface migration of the reactant. When the powders are not in contact, the reaction can occur only by vapor diffusion. It should be observed that the reactions discussed are heterogeneous. We introduce another heterogeneous reaction model after considering possible homogeneous reactions.

Homogeneous Reactions. Homogeneous reactions, because they are not restricted to an interface, tend to take place more rapidly than the corresponding uncatalyzed heterogeneous reactions. Since most solids have low vapor pressures, the homogeneous reaction in the vapor state may not be a major mechanism in reactions between two solids. If, however, the vapor pressure of the reactants is sufficiently high, as suggested by the detectable odor of ephedrine enantiomers, the vapor state reaction may provide a major mechanism by which the solids can react.

When the melting points of the reactants are reduced by the formation of a eutectic mixture to below the reaction temperature resulting in the formation of a liquid, a homogeneous reaction in the liquid phase becomes significant. When the liquid- and vapor-state reactions are the main mechanisms by which the product is formed, the following schemes can be used to describe the kinetics of formation of a racemic compound from a physical mixture of the enantiomers. It is assumed that

(a) the reaction via vapor or liquid state is faster than the reaction via surface migration;
(b) the two reactants have appreciable vapor pressures that are much greater than the vapor pressure of the product; and
(c) the equilibrium constant for the reaction, in which the two enantiomers react to give the racemic compound, is high, which means that the rate of the reverse reaction is insignificant.

Homogeneous Mechanism via the Vapor State

$$l \text{ or } d(\text{solid}) \rightarrow l \text{ or } d(\text{vapor}) \tag{8}$$

where l and d refer to the two enantiomers. The fugacities of the enantiomers in the vapor state are not equal to their saturated vapor pressures (and hence are not constants) because Eq. (8) does not represent an equilibrium. If the two enantiomers did not react in the vapor state to give the racemic compound, further sublimation of the solid enantiomer could proceed until the activities or fugacities of the enantiomer in the vapor and solid state become equal. Since the enantiomers react in the vapor state, for a given surface area, the fugacity of the enantiomer in the vapor state, at any time, is proportional to the number of moles of the enantiomer present in the solid state. Thus,

$$f_l = k_1 \cdot n_l \quad \text{and} \quad f_d = k_1 \cdot n_d \tag{9}$$

where f_l and f_d are the fugacities of the respective enantiomers in the vapor, n_l and n_d are the number of the moles of the respective enantiomers in the solid state, and k_1 is a proportionality constant which is the same for both the enantiomers. The reaction in the vapor state leading to the formation of the racemic compound, r, is given by

$$l(\text{vapor}) + d(\text{vapor}) \underset{k_5}{\overset{k_2}{\rightarrow}} r(\text{vapor}) \xrightarrow{k_3} r(\text{solid}) \tag{10}$$

where $k_3 \gg k_2$. It is possible that the vapors of the two enantiomers react directly to give the racemic compound, with rate constant k_5, without the intervention of r (vapor). The rate of formation of the racemic compound, r (or the rate of disappearance of each enantiomer, d and l, in the vapor state), is given by

$$dn_r/dt = k_2 \cdot f_l \cdot f_d \tag{11}$$

where k_2 (or k_5) is the second-order rate constant for the vapor state reaction and n_r is the number of moles of the racemic compound in the solid state. If, according to Eq. (9), the fugacity of the enantiomer in the vapor state is proportional to the number of moles of the respective enantiomer present in the solid state,

$$dn_r/dt = k_2 \cdot k_1^2 \cdot n_l \cdot n_d \tag{12}$$

Since l and d are enantiomers, $f_l = f_d$ when $n_l = n_d$. Equation (12) then reduces to

$$dn_r/dt = K_2 \cdot n_l^2 \tag{13}$$

where K_2 (which is equal to $k_2k_1^2$ or $k_5k_1^2$) is the overall second-order rate constant for the vapor-state reaction.

Homogeneous Reaction via the Liquid State

$$l \text{ or } d(\text{solid}) \rightarrow l \text{ or } d(\text{liquid}) \tag{14}$$

For two powders with a given specific surface area, the amount of liquid formed due to mutual contact is proportional to the number of moles of the substance present in the solid state. Thus,

$$a_l = k_1' \cdot n_l \quad \text{and} \quad a_d = k_1' \cdot n_d \tag{15}$$

where a_l and a_d and are the activities of the respective enantiomers in the liquid state and k_1' is a proportionality constant which is the same for both the enantiomers. The reaction between the two enantiomers leading to the formation of the racemic compound, r, is given by

$$l(\text{liquid}) + d(\text{liquid}) \underset{k_5'}{\overset{k_2'}{\rightarrow}} r(\text{liquid}) \xrightarrow{k_3'} r(\text{solid}) \tag{16}$$

where $k_3' \gg k_2'$. It is also possible that the two liquid enantiomers react directly to give the solid racemic compound, with rate constant k_5, without the intervention of r(liquid). The rate of formation of the racemic compound, r (or the rate of disappearance of each enantiomer, d and l, in the liquid state), is given by

$$dn_r/dt = k_2' \cdot a_l \cdot a_d \tag{17}$$

where k_2' (or k_5') is the second-order rate constant for the liquid state reaction and n_r is the number of moles of the racemic compound in the solid state. If, according to Eq. (15), the activity of the enantiomer in the liquid state is proportional to the number of moles of the respective enantiomer present in the solid state,

$$dn_r/dt = k_2' \cdot k_1'^2 \cdot n_l \cdot n_d \tag{18}$$

Since l and d are enantiomers, $a_l = a_d$ when $n_l = n_d$. Equation (18) then reduces to

$$dn_r/dt = K_2' \cdot n_l^2 \tag{19}$$

where K_2' (which is equal to $k_2'k_1'^2$ or $k_5'k_1'^2$) is the overall second-order rate constant for the reaction in the liquid state.

Parallel Homogeneous Reactions Involving Both the Vapor and the Liquid States

When the reaction takes place in both the liquid and the vapor states,

$$(dn_r/dt)_{\text{Total}} = (dn_r/dt)_{\text{Liquid State}} + (dn_r/dt)_{\text{Vapor State}} \tag{20}$$

The first and the second terms on the right-hand side of Eq. (20) are given by Eqs. (13) and (19), respectively, so that

$$(dn_r/dt)_{\text{Total}} = (K_2 + K_2')\, n_l^2 \tag{21}$$

Therefore, provided that the respective overall rate constants do not change, the reaction follows second-order kinetics even when both mechanisms operate simultaneously.

Heterogeneous Vapor–Solid Reaction

This heterogeneous reaction model arises from the concept developed for the above homogeneous reactions.

$$l(\text{solid}) + d(\text{vapor}) \xrightarrow{k_4} r(\text{solid}) \tag{22}$$

$$d(\text{solid}) + l(\text{vapor}) \xrightarrow{k_4} r(\text{solid}) \tag{23}$$

where k_4 is the rate constant for the vapor–solid (heterogeneous) reaction, which is the same for both these reactions for reasons of symmetry. Although the activity of the enantiomer in the vapor state is proportional to the number of

moles of the enantiomer in the solid state as indicated by Eq. (9), the activity of the solid enantiomer itself is a constant. Let the activity of the enantiomers in the solid state be a'_l and a'_d, respectively. According to the reactions represented by Eqs. (22) and (23), which must take place in parallel, the rate of formation of the racemic compound is given by

$$dn_r/dt = k_4 (a'_l \cdot f_d + a'_d \cdot f_l) \quad (24)$$

Since l and d are enantiomers, $a'_l = a'_d$. Furthermore, f_l and f_d are each proportional to the number of moles of the respective enantiomer present in the solid state as shown by Eq. (9) and $f_l = f_d$ when $n_l = n_d$. Since a'_l and a'_d are constants, Eq. (24) reduces to

$$dn_r/dt = K_4 \cdot n_l \quad (25)$$

where K_4 (which is equal to $2a'_l k_l k_4$) is the overall first-order rate constant for the vapor–solid heterogeneous reaction. Therefore, if the vapor–solid reaction is the main mechanism, the rate of formation of the racemic compound follows first-order kinetics.

ACKNOWLEDGMENTS

We thank Richard Brundage for advise on fitting the kinetic data to a kinetic model and Daniel Adsmond and Raj Suryanarayanan for critically commenting on the manuscript.

REFERENCES

1. H. G. Brittain. Crystallographic consequences of molecular dissymmetry. *Pharm. Res.* 7:683–690 (1990).
2. A. J. Repta, M. J. Balteza, and P. C. Bansal. Utilization of an enantiomer as a solution to a pharmaceutical problem: Application to solubilization of 1,2-di(4-piperazine-2,6-dione)propane. *J. Pharm. Sci.* 65:238–242 (1975).
3. S.-T. Liu and A. Hurwitz. Effect of enantiomeric purity on solubility determination of dexclamol hydrochloride. *J. Pharm. Sci.* 67:636–638 (1978).
4. W. F. Schmidt, W. Porter, and J. T. Carstensen. Thermodynamics in the prediction of the solubilities of binary mixtures of the diastereomers and enantiomers of ephedrine. *Pharm. Res.* 5:391–395 (1988).
5. A. J. Romero and C. T. Rhodes. Approaches to stereospecific preformulation of Ibuprofen. *Drug. Dev. Ind. Pharm.* 15:777–792 (1991).
6. D. J. W. Grant and T. Higuchi. *Solubility Behavior of Organic Compounds,* John Wiley & Sons, New York, 1990, pp. 12–88, 307–354.
7. D. Z. D'Argenio and A. Schumitzky (eds.). *ADAPT II User's Guide,* Biomedical Simulations Resource, University of Southern California, Los Angeles, 1990.
8. D. Z. D'Argenio and A. Schumitzy. A program package for simulation and parameter estimation in pharmacokinetic systems. *Comput. Prog. Biomed.* 9:115–134 (1979).
9. I. Prigogine and R. Defay. *Chemical Thermodynamics* (D. H. Everett, translator), Longman, London, 1954, p. 375.
10. J. Jacques, A. Collet, and S. H. Wilen. *Enantiomers, Racemates and Resolutions,* John Wiley & Sons, New York, 1981, pp. 4, 88–100.
11. S. R. Byrn. *Solid State Chemistry of Drugs,* Academic Press, New York, 1982, pp. 59–74, 321.
12. J. T. Carstensen. *Drug Stability,* Marcel Dekker, New York, 1990, pp. 129–163.
13. R. P. Rastogi, N. B. Singh, and R. P. Singh. Organic solid state reactions. *J. Solid State Chem.* 20:191–200 (1977).
14. R. P. Rastogi, N. B. Singh, and R. P. Singh. Organic solid state reactions. II. Kinetics of 8-hydroxyquinoline with maleic anhydride, succinic anhydride, phthalic anhydride, catechol & resorcinol. *Ind. J. Chem.* 15A:941–946 (1977).
15. R. N. Galante, A. J. Visalli, and D. M. Patel. Solid state acetylation of codeine phosphate by aspirin. *J. Pharm. Sci.* 12:1494–1497 (1979).
16. G. M. Frankenbach. *The Preparation and Characterization of Hydrogen-Bonded Cocrystals with Applications to Material Science,* Ph.D. thesis, University of Minnesota, Minneapolis, 1989.