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Investigation of piroxicam polymorphism

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Summary

The polymorphism of piroxicam has been discussed by many authors, but it is still uncertain in how many polymorphic and pseudopolymorphic modifications it can exist. The results of DSC and IR analyses confirm that simple crystallization from different solvents yields modifications designated as I and II and monohydrate. Depending on the cooling rate of the piroxicam melt, amorphous or metastable polymorphic forms referred to as III and IV were obtained.

Introduction

Most active substances used in pharmacy exist in more than one polymorphic modification. The first review of pharmaceutical applications of polymorphism was published by Haleblian and McCrone (1969). One of the most relevant differences among polymorphic modifications of certain active substances is the difference in their solubility and dissolution rate. These differences can also affect their bioavailability.

Commonly, metastable polymorphic modifications of active substances show higher solubility and dissolution rate in comparison with stable ones. Normally, solutions of metastable modifications are supersaturated as compared to those of stable types; precipitation of a less soluble stable modification from such solutions can be observed. This represents a serious limitation for the usage of polymorphism as a tool for improving solubility and dissolution rate. However, the usage of metastable polymorphs is also limited because of their instability in the solid state (Shefter, 1981).

A great number of registered active substances have been screened for polymorphism. One example is piroxicam, a highly potent anti-inflammatory agent, known for its low solubility and dissolution rate under acidic conditions in which its absorption takes place (Hertzfeldt and Kummel, 1983).

Piroxicam polymorphism has been discussed since 1982, and today it is still uncertain in how many modifications it can exist. Different procedures (crystallisation from solvents and from a melt) for preparation of polymorphic modifications and also different analytical techniques (DSC, X-ray, IR, etc.) for their characterisation have been described in the literature. The most extensive review on the physico-chemical properties of piroxicam modifications was published by Mihalić et al. (1982, 1986), reporting two polymorphic and one pseudopolymorphic (monohydrate)

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modification. Polymorphic modifications differ in their IR spectra, X-ray diffraction and melting points. Some physico-chemical properties (X-ray diffractometry, SEM, IR spectroscopy and dissolution behaviour) of anhydrous piroxicam (white) and its monohydrate (yellow) were described by Kozjek et al. (1985); the IR spectral and X-ray diffraction data for monohydrate differed from those reported by Reck et al. (1988).

Three polymorphic modifications of piroxicam produced by fast cooling of its melt were discovered by Kuhnert-Brandstaetter and Vollenklee (1985). The melting point and the IR spectrum of the modification they designated as I coincide with those of the metastable modification reported by Mihalić et al. (1982, 1986).

By following published data on piroxicam poly- and pseudopolymorphism, we have tried to prepare modifications by crystallization from a number of solvents and through melt cooling. For polymorph characterization, we have used differential scanning calorimetry (DSC), IR spectroscopy (IR) and thermogravimetry (TG).

Experimental

Substances

Piroxicam (Fig. 1) (4-hydroxy-2-methyl-*N*-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide), produced by KRKA Pharmaceuticals (Yugoslavia) was used as received.

The solvents used for crystallization were as follows: acetone p.a. (Kemika, Zagreb, Yugoslavia); ethanol (concentrated and absolute) p.a. (Alkaloid, Skopje, Yugoslavia); chloroform p.a., for chromatography (Kemika, Zagreb, Yugoslavia), stabilised with max. 1% ethanol; dioxane p.a. (Alkaloid, Skopje, Yugoslavia), stabilised with 25 ppm

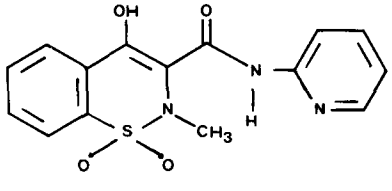

Fig. 1. Structure formula of piroxicam.

2,6-di(*tert*-butyl)-4-methylphenol; methanol (concentrated and absolute) p.a. (Kemika, Zagreb, Yugoslavia); and methylene chloride p.a. (Kemika, Zagreb, Yugoslavia).

Methods

Methods of preparation

Crystallization An appropriate amount of piroxicam was dissolved in boiling solvent and the solution cooled in a refrigerator at 4 °C or in a freezer at −20 °C. After 24 h, crystals were removed by filtration and dried in vacuo at room temperature. All samples were sieved through a 125 μm sieve.

Cooling of the piroxicam melt An appropriate amount (about 2.5 mg) of piroxicam was weighed in an aluminium sample pan and closed with the cover. The pan was put into a DSC sample cell and heated to 207 °C. Immediately after reaching this temperature, the sample was cooled to 0 °C at two different cooling rates: 320 and 10 K/min. The melting and cooling were performed under a dynamic atmosphere of nitrogen at a rate of 40 ml/min.

Analytical methods

Thermal analysis Thermograms were recorded on Perkin-Elmer DSC-4 Thermal Analyser with a 3700 Data Station. Samples of 1–5 mg were closed in aluminium pans with a hole in their covers.

IR spectroscopy IR spectra were recorded from KBr pellets (1.5 mg piroxicam mixed with 143.5 mg dried KBr) on a Perkin-Elmer 257 IR spectrophotometer.

Results and Discussion

Thermograms of piroxicam crystallized from different alcohols are shown in Fig. 2: there are two endothermic peaks representing melting of the two polymorphic modifications. The onset melting temperatures and melting enthalpies are listed in Table 1. Modifications with a lower melting point are denoted II and those with the higher values as I. The thermograms clearly show that melting of modification II is followed by crystallization of modification I from its melt.

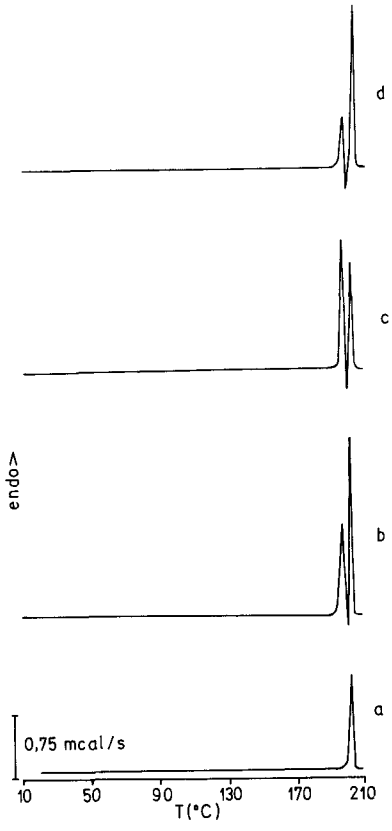

Fig. 2. DSC of micronized piroxicam (a) and piroxicam crystallized from: ethanol (b), methanol (c) and *n*-propanol (d).

As is well known (Mihalić et al. 1982, 1986), the most significant differences in the IR spectra of different polymorphic piroxicam modifications concern the positions of the amide -NH or enol -OH stretching absorption bands at 3385 cm^{-1} for modification II (needle form) and 3300 cm^{-1} for modification I (cubic form). Because of this, in combination with the very small differences in the fingerprint region of the spectrum, only a part of the spectra (from 2500 to 4000 cm^{-1}) was used for comparison. In our IR spectra amide or enol absorption bands were shifted 30 cm^{-1} to higher wave numbers (to 3415 and 3360 cm^{-1}). From the IR spectra of piroxicam crystallized from different alcohols it is possible to conclude that it crystallizes in modification II (Fig. 3).

The DSC results in Figs 2 and 3 show that the melt of modification II is thermally unstable, giv-

TABLE 1

Onset temperatures and melting enthalpies of piroxicam samples crystallized from different solvents

Sample crystallized from	T_{mI} (°C)	ΔH_{mI} (J/g)	T_{mII} (°C)	ΔH_{mII} (J/g)
Methanol	195.1	88.0	201.6	38.4
Absolute methanol	193.8	41.2	201.0	77.5
Ethanol (96 vol.%)	195.8	80.2	201.1	47.9
Absolute ethanol	195.3	68.7	201.1	70.6
n-Propanol	194.2	33.7	200.6	97.7
Chloroform			201.6	111.7
Methylene chloride	195.1	5.8	201.3	133.2
Methylene chloride after 6 days	195.1	5.8	201.3	133.2
Acetone	195.9	82.7	201.8	29.7
Dioxane			201.6	128.7
Ethanol/water (1:1)			201.1	121.2
Methanol/acetone (1:1)	194.3	9.0	201.1	123.4
Ethanol/chloroform (1:1)	195.4	11.2	201.3	116.9
Water			201.0	124.7

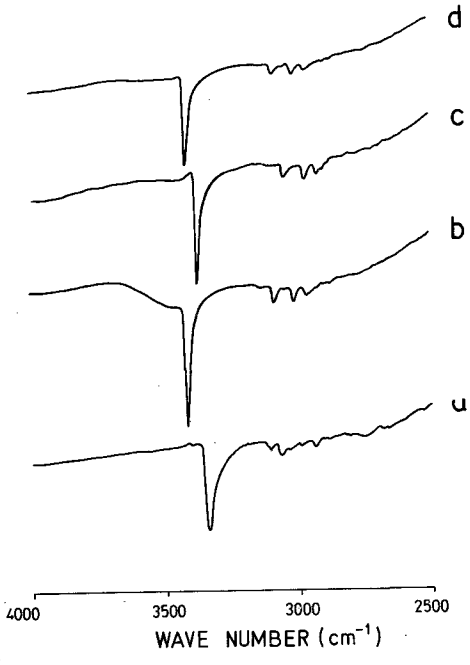

Fig. 3. IR spectra of micronized piroxicam (a) and piroxicam crystallized from: ethanol (b), methanol (c) and *n*-propanol (d).

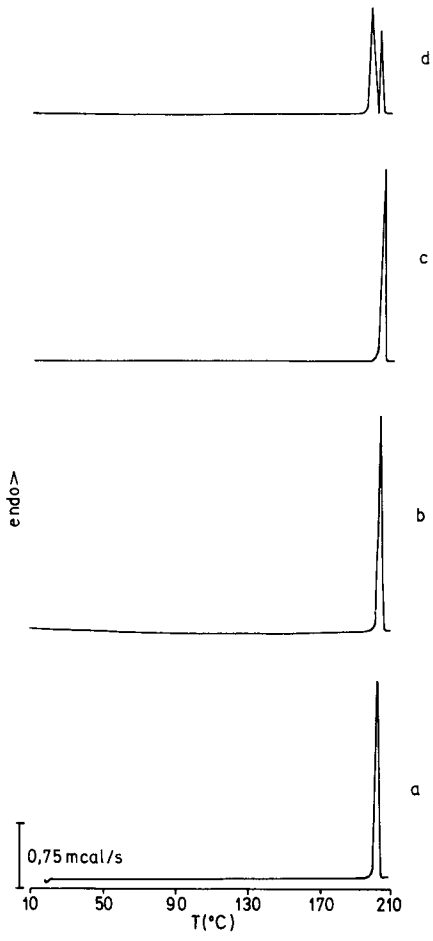

Fig. 4. DSC of micronized piroxicam (a) and piroxicam crystallized from: dioxane (b), chloroform (c) and acetone (d).

ing rise to modification I after crystallization. No solid polymorphic transition of II to I within 1 week was observed at room temperature.

Piroxicam crystallization from chloroform and dioxane solutions gives crystals of pure modification I (Figs 4 and 5). Also modification II crystallizes from acetone solution. It is interesting that crystallization from methylene chloride solution also yields modification II (Figs 6 and 7). Furthermore, a mixture of both modifications is obtained from mixed solvents: methanol/acetone (1 : 1) and ethanol/chloroform (1 : 1) (Figs 8 and 9).

In Table 1, the melting points and melting enthalpies of piroxicam crystallized from the solvents mentioned in Figs 2–11 are collected. It

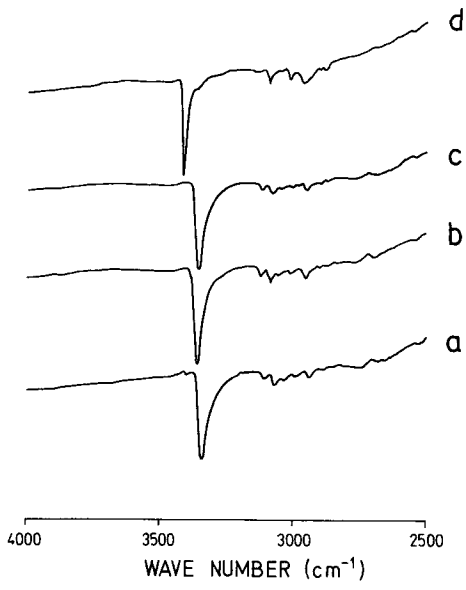

Fig. 5. IR spectra of micronized piroxicam (a) and piroxicam crystallized from: dioxane (b), chloroform (c) and acetone (d).

can be seen that the melting point of modification II is $195 \pm 0.69\,^{\circ}C$ and that of modification I $201.3 \pm 0.32\,^{\circ}C$. In contrast to small deviations in the melting point of piroxicam crystallized from different alcohols, large differences in the melting enthalpies were found. There are significant differences in the computed melting enthalpies for

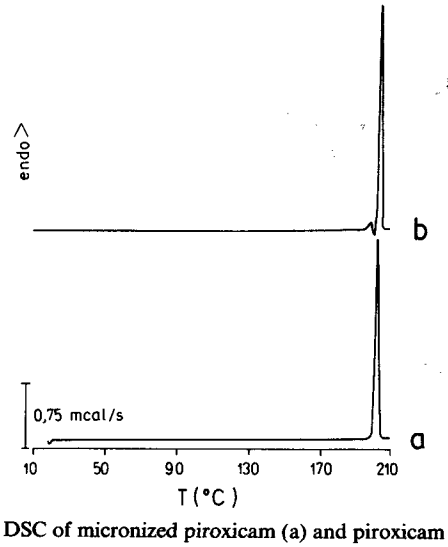

Fig. 6. DSC of micronized piroxicam (a) and piroxicam crystallized from methylene chloride (b).

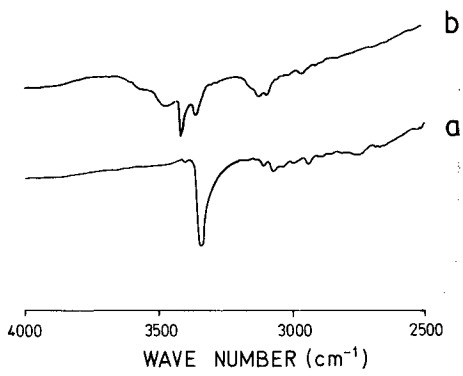

Fig. 7. IR spectra of micronized piroxicam (a) and piroxicam crystallized from: methylene chloride (b).

both modifications (I and II). One possible factor influencing the computation of melting enthalpies is the competition between melting of modification II and crystallization of modification I from its melt. Experiments aimed at clarifying these variations in melting enthalpies are currently in progress.

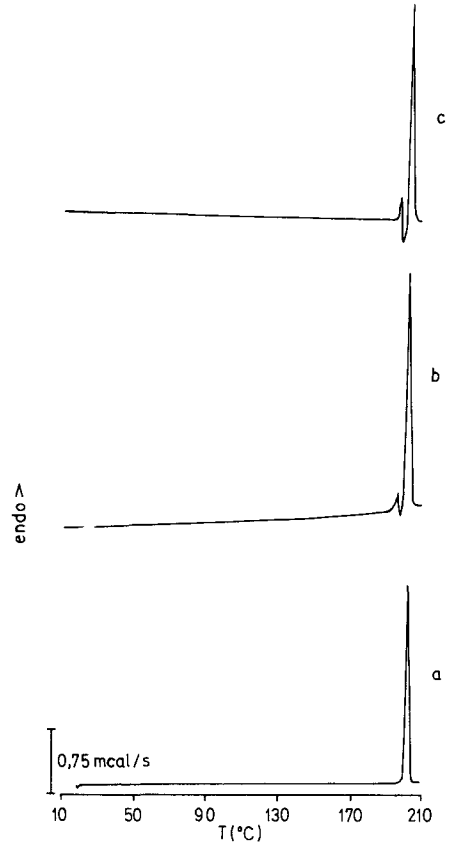

Fig. 8. DSC of micronized piroxicam (a) and piroxicam crystallized from: methanol/acetone (1:1) (b) and ethanol/chloroform (1:1) (c) mixtures.

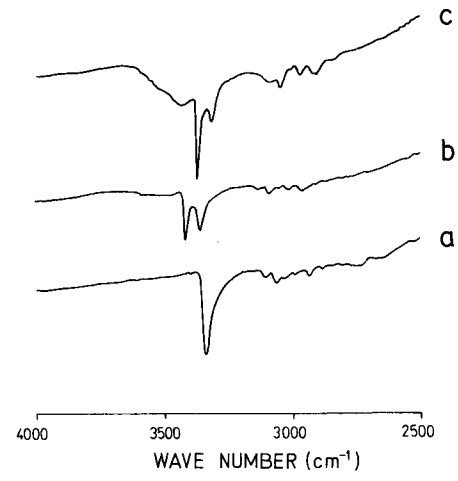

Fig. 9. IR spectra of micronized piroxicam (a) and piroxicam crystallized from: methanol/acetone (1:1) (b) and ethanol/chloroform (1:1) mixtures (c).

From the experimental data discussed above, it can be concluded that the polarity of the solvent plays an important role in the crystallization of piroxicam. Modification II crystallizes from polar solvents and modification I from nonpolar solvents. An exception to this rule is the crystallization from water, giving the monohydrate as has

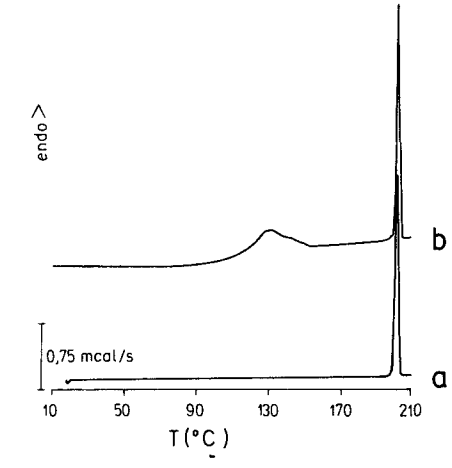

Fig. 10. DSC of micronized piroxicam (a) and piroxicam crystallized from water (b).

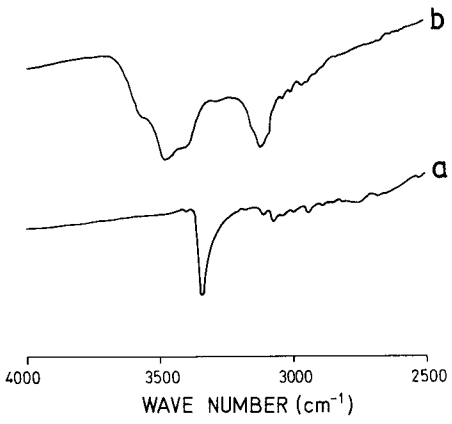

Fig. 11. IR spectra of micronized piroxicam (a) and piroxicam crystallized from water (b).

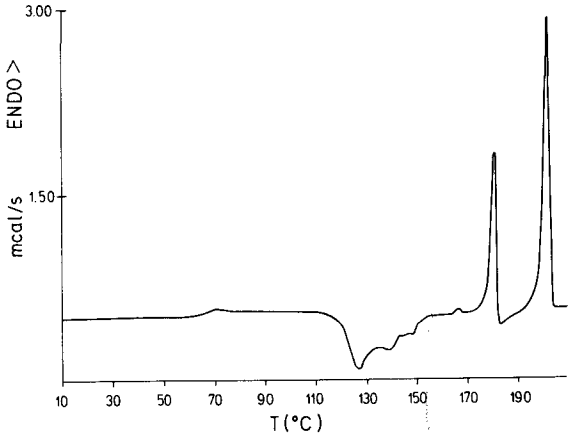

Fig. 12. DSC of the piroxicam melt cooling (A) and piroxicam sample submitted to a second heating cycle after slow cooling of its melt to 20 °C.

been described in the literature and also confirmed by our thermogravimetric and elemental (CHN) analyses. It is worth mentioning that the thermal behaviour of piroxicam monohydrate after removal of crystal water is the same as that of modification I; the melting points are practically the same (Table 1 and Fig. 10). These findings are inconsistent with literature data (Kozjek et al., 1985). However, there are significant differences in the whole IR spectrum of modification I and monohydrate (Fig. 11).

Comparison of our IR spectra with published examples (Kozjek et al., 1985) shows that the latter for the monohydrate is comparable to the spectrum of modification II. These findings are in accordance with those of Reck et al. (1988).

The thermal behaviour of the piroxicam melt submitted to slow cooling was subsequently studied. At a slow rate of cooling (10 K/min), the piroxicam melt crystallizes between 140 and 90 °C (onset temperature 138.4 °C) to modification III (Fig. 11) with an onset melting temperature of 175.7 °C. This melting point is comparable to that for modification II determined using hot-stage microscopy by Kuhnert-Brandstaetter and Vollenklee (1985). The values of the enthalpies of crystallization and melting of modification III are comparable (−81.5 J/g for crystallization and 87.8 J/g for melting).

It is known (Kuhnert-Brandstaetter and Vollenklee, 1985) that rapid cooling of a piroxicam melt yields two modifications (designated by those authors as III with m.p. 160–163 °C and II with m.p. 175–179 °C). Crystallization of modification I (m.p. 195–199 °C) from the melt of modification II was reported by the same authors (1985). These melting points were determined using a hot-stage microscope. In our experiment very fast cooling was also used (320 K/min) to 0 °C. After 5 min a new heating cycle was started (Fig. 12). A significant difference between slowly and 'shock' cooled piroxicam melts was observed. After shock cooling, a glass transition point (midpoint 63.6 °C) was obtained on reheating. From this transition, it was concluded that piroxicam exists in an amorphous state. When such a shock cooled sample was heated beyond the glass transition, crystallization was observed. Modifications III and IV were identified (Table 2 and Fig. 13). It is interesting that modification III is thermally stable when produced by slow cooling. Crystallization similar

TABLE 2

Onset temperatures and melting enthalpies of piroxicam polymorphic modifications produced by shock cooling of piroxicam melt

Modification	T_m (°C)	H_m (J/g)
II	199.2	19.2
III	178.4	9.3
IV	164.1	0.3

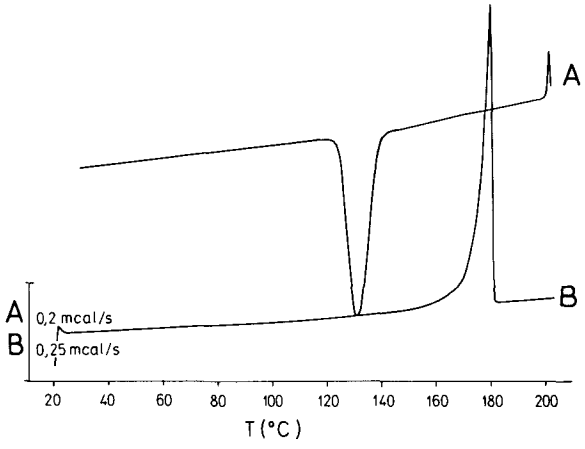

Fig. 13. DSC of piroxicam sample submitted to a second heating cycle after shock cooling of its melt to 20 °C.

to that described by Kuhnert-Brandstaetter and Vollenklee can be observed in thermograms of piroxicam samples heated after shock cooling of the melt to 0 °C. The melting points of our modifications III and IV are comparable to those reported by Kuhnert-Brandstaetter and Vollenklee (1985) for modifications they designated as II and III.

We have tried to produce a similar sample (shock cooled) in larger quantities, however, the melted piroxicam was not stable enough for this purpose (Kerč et al., 1989).

Conclusion

The physical state of piroxicam has been described and discussed by many authors, however, several unanswered questions remain. The results of the present experiments enabled us to draw the following conclusions:

(a) piroxicam exists in four polymorphic forms and at least one pseudopolymorphic modification (I, m.p. 201.6; II, m.p. 195.5; III, m.p. 178.4 °C; IV, 164.1 °C);

(b) by simple crystallization from different solvents only modifications I, II and the monohydrate can be obtained;

(c) the melt of modification II is thermally unstable, giving modification I after recrystallization;

(d) the polarity of the solvent has a strong influence on the physical state of the crystallizate: from polar solvents containing small quantities of water, metastable modification is obtained and from nonpolar solvents modification I;

(e) fast cooling of piroxicam melt gives rise to the amorphous state;

(f) on heating the amorphous state above the T_g modifications IV, III and I crystallize.

Acknowledgments

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