Optical Spectra and Magnetic Susceptibility of Two Different Salts of Several Phenothiazine Derivatives

A. ORTIZ, A. GONZALEZ, AND J. I. FERNANDEZ-ALONSO

Departamento de Quìmica-Fìsica y Quìmica Cuantica, Centro Coordinado CSIC-UAM Facultad de Ciencias C-XIV, Cantoblanco, Madrid 34, Spain

Two different salts, perchlorates and bromides, of six phenothiazine derivatives substituted in R_2 and R_{10} were prepared. Magnetic susceptibility and diffuse reflectance have been used to study the contribution of the different substituents R_2 and R_{10} and the counter anions to the electronic properties of these compounds in the solid state. Within a type of salt, the R_2 substituents are capable of producing a variation of χ_m depending on their electron-donating or electron-withdrawing power upon the π electronic structure of the phenothiazine nucleus. Between the two types of salts it can be seen that the χ_m varies as the counteranion size varies. The effect produced by the R_{10} depends on the counter anion size. These characteristics are also shown in the charge-transfer band in the solid state.

Introduction

Phenothiazine and its derivatives are diamagnetic molecules. Oxidation of these products gives cation radicals with an unpaired π electron. These odd-electron species seem to play an important role in biochemical processes (*1*). In addition, many dyestuffs, such as methylene blue, are oxidation products of substituted phenothiazines. Although there has been plenty of work made on the radical cation of phenothiazine and its derivatives in solution (*2, 3*) not much work has been produced on the solid state of these radicals. In general, solid ion-radical salts have been of great interest because the ion-radical molecules form plane-to-plane stacking into columns so as to make a large overlap between the half-filled π orbitals of each radical forming energy bands belonging to the crystalline complex (*4*). The solid phase of these can be described thus:

$$(Q+ \ldots Q+ \ldots Q+ \ldots Q+ \ldots)$$
$$(Q^0 \ldots Q^- \ldots Q^0 \ldots Q^{2+} \ldots Q^0 \ldots),$$
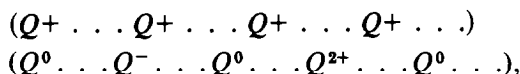
where each Q+ is a cation radical.

Much knowledge regarding mutual charge-transfer interaction has been accumulated by measuring solid-state spectra and magnetic susceptibilities (*5*). However, no systematic comparisons have been reported on solid-state properties, and, as phenothiazine radical is similar to the organic conductor MP-TCNQ, where the MP is the 14 π electron cation N-methylphenazinium, phenothiazine and its derivatives provide us with a series of compounds which fulfill the requirements of isomorphism and isostoichiometry to allow us to obtain relationships between structure and physical properties.

As the paramagnetism of these radical salts based on phenothiazine cation radicals

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TABLE I

STRUCTURAL CHARACTERISTICS OF THE PHENOTHIAZINE DERIVATIVES STUDIED

Compound	R_2	R_{10}	Salt
I Promazine	–H		ClH[a]
II Trifluorpromazine	–CF$_3$	$CH_2-CH_2-CH_2-N\overset{CH_3}{\underset{CH_3}{}}$	ClH[c]
III Clorpromazine	–Cl		ClH[b]
IV Metopromazine	–OCH$_3$		Maleate[b]
V Proclorperazine	–Cl	$CH_2-CH_2-CH_2-N\bigcirc N-CH_3$	ClH[d]
VI Perfenacine	–Cl	$CH_2-CH_2-CH_2-N\bigcirc N-CH_2CH_2OH$	ClH[e]

[a] Rhodia.
[b] Specia.
[c] Squibb.
[d] Upjohn.
[e] Schering USA.

and closed-shell diamagnetic counter ions like ClO$_4^-$ and Br$^-$ are clearly associated with the phenothiazine nucleus, they provide us with a simpler case to study CT complexes, where the magnetic properties are associated with only one stack, then the TTF-TCNQ complexes which have two types of stacks and the respective contribution is more difficult to ascertain.

Electronic absorption spectra and magnetic susceptibility, which have traditionally been the most popular tools for elucidating the electronic structure of molecules and solids should be able to produce some information concerning the interaction in these solid radical salts.

We report here the preparation and solid-state properties (CT and χ_m) of a series of phenothiazine derivatives. We also examine how the R_2 and R_{10} substituents, as well as the counter anions, seem to contribute to the solid-state properties of these cation-radical salts.

Experimental

(A) Compounds

The phenothiazine derivatives studied are listed in Table I and were supplied by various pharmaceutical laboratories. Their general formula is shown in Fig. 1.

Perchlorates. In order to obtain the cation radicals in the solid state the Merkel method was used (6). The melting points of the salts ranged between 170 and 224°C. The uv and visual spectra of these products in solution were given in a previous work (7). The cation radicals are stable in the presence of air indefinitely, and no change is experienced in their composition or properties even after a considerable length of time. The elemental analysis (%) of these compounds is:

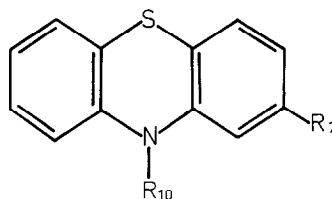|	
Prochlorperazine	C: 41.25, S: 5.18, H: 4.43, Cl: 17.84
Metopromazine	C: 41.35, S: 6.04, N: 5.40, H: 4.71, Cl: 12.60
Promazine	C: 40.65, S: 6.38, N: 5.58, H: 4.82, Cl: 14.12

FIG. 1. Molecular structure of phenothiazine.

Perfenazine	C: 40.56, S: 5.16, N: 6.76, H: 4.70, Cl: 17.10
Trifluorpromazine	C: 37.04, S: 5.62, N: 4.91, H: 3.89, Cl: 12.43
Chlorpromazine	C: 38.04, S: 5.97, N: 5.22, H: 4.3, Cl: 19.81.

These values agree with the formula proposed by Merkle.

Bromides. The bromide cation radicals were prepared by oxidation with bromine of the organic compounds dissolved in acetic acid, as described by Kerhmann and Diserens (8). The elemental analysis gives:

Chlorpromazine	C: 32.03, H: 2.99, S: 5.02, Cl: 5.55, N: 4.44.
Promazine	C: 33.80, H: 3.34, S: 5.31, N: 2.98, Br: 52.91.
Metopromazine	C: 34.10, H: 3.50, N: 4.42, S: 5.06, Br: 50.41
Perfenazine	C: 34.98, H: 3.62, N: 5.81, S: 4.43, Br: 44.05.
Trifluorpromazine	C: 32.64, H: 2.85, S: 4.77, N: 4.17, Br: 47.56.
Prochlorperazine	C: 34.64, H: 3.49, Br: 46.08, S: 4.62, N: 6.06.

From this analysis the bromine content is as high as 4 Br for each PHT molecule. Also the melting points of these cation radicals are not fixed but give lower values as time passed, probably due to loss of bromine during storage. From this, and as described by Doi. for phenothiazine (9), it is deduced that it is not possible to obtain a unique cation-radical bromide, but a mixture of this cation with tribromide. Therefore, the constitution of the products ob-tained with bromine oxidation may be considered to be a mixture of the materials indicated.

(B) R.D. Spectra

A Beckman DK-2A with a corresponding attachment was used. Wavelength ranged from 400 to 1500 nm. The radiation source was a tungsten lamp and the detector was lead sulfide. Pure samples were used as well as samples where the salt under analysis was dissolved in an optically inert KBr matrix. The ratio between the cation radical and solvent was 1 : 200. The spectra were recorded as the difference of absorbance between the mixture and pure potassium bromide.

(C) χ Measurements

Paramagnetic susceptibilities were determined by the Faraday method. Samples in powder form were tightly packed in a quartz tube 4 mm in diameter and 8 mm in height. The tubes were suspended between constant-gradient pole pieces of a B-M6 Bruker electromagnet by a thin quartz fiber from the beam of a 4411 Sartorius electro-balance. The force acting on each sample, which weighed approximately 0.06, and 0.07 g, was of the order 10^{-2}–10^{-3} μg, depending on the magnetic field H in a 3-cm gap with polar pieces HdH/dX = 21.54 KG/cm for 30 A and HdH/dX = 12.21 KG/cm for 20 A. For the elimination of ferromagnetic impurities, χ was obtained from (χ, $1/H$) plot by extrapolation of χ to $1/H = \infty$. Slopes of the order of 10^{-3}–10^{-4} G were obtained; i.e., the samples contained relatively low concentrations of fer-romagnetic impurities with reference to the standard sample used, which was $C_{10}H_{22}$ (Merck). For this a value of χ = 0.8523 × 10^{-6} cgs was taken (10).

Each sample was measured 10 times at two different field strengths (13.35 and 10.33 KG) in a vacuum of 10^{-2} Torr. The

accuracy of the measurements of χ is believed to be $\pm 1\%$.

Results

(A) Magnetic Susceptibility

It is known that the charge transfer interaction between ion radicals produces a marked decrease in the paramagnetic susceptibilities of these salts (11,12). This seems to agree with the present cations. The diamagnetic contribution was estimated from the value of diamagnetic susceptibilities of components on the assumption that the value for a neutral organic molecule may be used in place of the molecular ion. (However, when the neutral organic molecule is changed into an ion, it may become coplanar and this would result in a little increase in diamagnetic susceptibility). The values for the phenothiazine derivative were taken from Pascal's constants and for ClO_4^- and Br^- from Mulay (13).

The χ_m values of perchlorates given in Table II show a clear dependence on the R_2 substituents, being the most paramagnetic

the compound with $R_2 = -H$ and the least the one with $R_2 = -OCH_3$; a secuence of the χ_m values can be extracted as follows:

$$-H > -CF_3 > -Cl > -OCH_3;$$
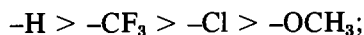
this must be related to different interaction degree of the radicals in the solid state due to the R_2 substituents, which must be able of modifying considerably the spin overlap of the unpaired π electron, because of their electron-donating ($-OCH_3$) or electron-withdrawing ($-CF_3$) power upon the π structure of the phenothiazine nucleus.

For products with $R_2 = -Cl$ and different R_{10}, χ_m values are very similar, so there seems to exist no influence of such substituents upon the magnetic susceptibility.

The χ_m susceptibility at different temperatures of some perchlorate radical cations show that these compounds are normal paramagnetics, with an increase of χ as T decreases.

For the bromides, the same relation expressed above can be considered to exist. However, the χ_m difference between the $-CF_3$ and $-Cl$ is not so evident as it is with

TABLE II

MAGNETIC SUSCEPTIBILITY OF THE PERCHLORATE AND BROMIDES OF THE PHENOTHIAZINE DERIVATIVES

	Compounds	MW	Observed susceptibility at 294K (cgs/mole)$\chi_\infty 10^{-6}$	Assumed diamagnetism (cgs/mole)$\chi_d(-10^{-6})$	Paramagnetic susceptibility (cgs/mole)$\chi_m \times 10^{-6}$	Radical concentration (%)
ClO_4^-	Promazine	502.25	1.340	257.50	930.45	86
	Trifluorpromazine	570.24	1.036	293.57	880.92	83
	Clorpromazine	536.74	0.3563	288.89	529.3	64
	Metopromazine	532.24	0.02932	273.9×10^{-6}	289.5	47.8
	Proclorperazine	591.74	0.196	325.190	441.196	59
	Perfenazine	621.74	0.266	341.660	507.084	63
Br^-	Promazine	603.91	0.352	302.30	514.67	63.8
	Trifluorpromazine	671.90	0.0004	338.37	338.57	51.7
	Clorpromazine	638.40	0.063	330.75	370.96	54
	Metopromazine	633.90	−0.380	318.76	77.90	24.8
	Proclorperazine	693.56	0.0613	367.05	409.35	56
	Perfenazine	723.39	−0.052	383.52	346	52.2

the perchlorates. This can be explained in terms of the capacity of polarizability of the radical cations. This polarizability depends strongly on the R_2 substituents. The electron-withdrawing effect of the $-CF_3$ substituent is capable of producing a strong polarization in the radical cation (14). This will tend to reduce the Coulomb repulsion between the free electrons of adjacent radical cations. Consequently the interaction will be stronger and the paramagnetism of these cations will decrease.

Counter anions. The steric effect of the counter anions is very important because the repulsions and interaction between the charges depend on the separation between two adjacent radicals and this distance is also a consequence of the size of the counter anions. Therefore as the steric effect in the bromides is reduced compared to ClO_4^- the polarization of each radical manifest more strongly in these products and consequently their χ_m values are lower than the corresponding perchlorates. The polarization effect of $-CF_3$ on the phenothiazine nucleus, shows strongly in the bromides, where the minor steric effect of the Br^- produces a considerably lower χ_m values than the corresponding perchlorates and even similar to the $-Cl$ bromides derivatives.

Therefore, these products are paramagnetic with 86–47% free unpaired electrons for perchlorates and 63–24% for bromides. The difference between these two series of paramagnetic values must be related to the interaction of the radicals in the solid state which can be attributed to the steric effect of the counter anions upon these interaction. Also the different paramagnetic values within a series must be related to the different interaction degree of the radicals in the solid state due to the R_2 substituents. Consequently, these substituents show a strong effect on the χ_m of the compounds, perchlorates, and bromides. It may be that the spin exchange interactions in these solids are

not restricted to those of bimolecular nature. On the contrary, it seems to be spread over several radicals, probably through a linear array of radical cations (12).

Although it is not clear at present whether the spin-exchange interaction can be described by a singlet–triplet model, it can be seen that the charge-transfer interaction between cation radicals makes a significant contribution to the antiferromagnetic spin-exchange interaction.

A qualitative explanation can be made by considering, following Hausser and Murrell (15), a particular pair of adjacent radicals in a chain. The interaction of this pair gives rise to singlet (nonmagnetic) state, and a triplet (magnetic) state, for which the relative position are determined, to a first approximation, by an exchange integral between the paired radicals.

If the singlet–triplet excitation energy, to which the spin exchange in the charge-transfer contributes, is small, the triplet state may become thermally accessible and paramagnetism can be observed. Therefore, in a linear array of radicals, charge transfer configurational interactions also contribute to the determination of the relative energy levels of the magnetic and nonmagnetic states. Consequently, it appears that the spin-exchange coupling parameter will depend on the relative energy of the exchange interaction and on charge transfer configurational interaction effects (16).

All these effects are evident in the products studied. First, the singlet–triplet excitation energy seems to be smaller in the bromides, therefore, the paramagnetism decreases accordingly, and second, the R_2 substituents, modify the charge transfer configurational interactions, and, consequently, the energy levels of the magnetic and nonmagnetic states, are also modified.

(B) R.D. Spectra

It is clear that the crystalline spectra arise from CT interactions between ion rad-

icals. These spectra have been proved to have a close relationship with the electrical and magnetic properties. Here the covalent force binds the radicals close to each other; however, the exchange repulsions of the closed-shell electrons and the steric repulsion increase the radical distances, and there is as well the positive charge on each radical which is repulsive. Nevertheless, the actual packing structure represents a counterbalance of all these opposite forces.

In order to study the solid-state spectra, a comparison was made with the visible spectrum of the cation radical of chlorpromazine in solution (Fig. 3e). This cation in $9N$ sulfuric solution presents the following maxima:

λ(nm) ϵ λ(nm) ϵ λ(nm) ϵ

525 (8450),   760 (1200),   840 (1130)

The maxima of each derivative radical cation varies slightly depending on the batochromic or hipsochromic effect of the R_2 substituents (7) and the ϵ values are similar to the above. The bromides present the same radical spectra, however, the maxima is strongly displaced toward the red zone, thus, in chlorpromazine bromide are at 575 nm and 762–862 nm the vibrational structure. The ϵ values are similar; the displacement of the band must be due to the substitution of an –H in the phenothiazine nucleus by an Br.

1. R_2 Effect

(a) The ClO_4^- cation radicals. The diffuse reflection spectra of these products contain two bands, one at 500 nm and a very wide one of varying intensity from 600 to 1200 nm; from 1200 to 2500 nm there is no other transition, though in some cases, such as curve b and c of Fig. 2 and curves a and b of Fig. 3 there is a strong absorption, however, no maximum was obtined up to 2700
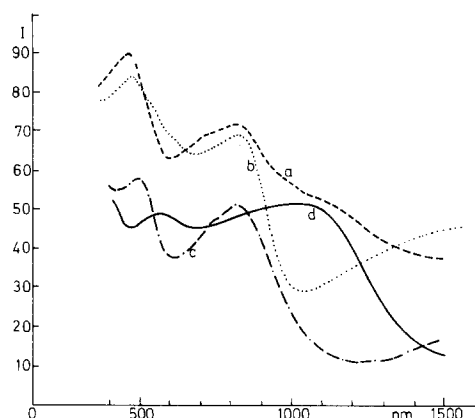

FIG. 2. Diffuse reflectance spectra of solid-state spectra of the perchlorates of: (a) promazine, (b) trifluorpromazine, (c) chlorpromazine, and (d) metopromazine.

nm unfortunately, our spectrophotometer could not be applied to the region below 2700 nm.

The position of the first band corresponds with the spectrum of the same radical in solution (Fig. 3) at 525 nm, although it is slightly displaced towards the blue zone. These transitions of the monomer seem to be affected by the field of the other cations which cause a shift in the $\pi \rightarrow \pi^*$ bands.
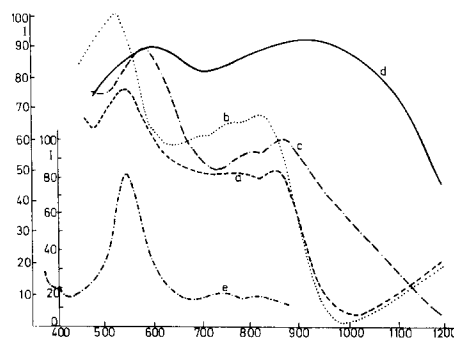
The second band is wide and of varying

FIG. 3. Diffuse reflectance spectra of the bromides: (a) promazine, (b) trifluorpromazine, (c) chlorpromazine, (d) metopromazine; (e) visible spectrum of chlorpromazine in $9N$ sulfuric acid solution. (The inner ordinate axis corresponds to the chlorpromazine visible spectrum.)

intensity, exhibiting typical characteristics of a charge-transfer band: wide and not very well defined maxima. Therefore, this transition can be considered as a charge transfer band produced by interaction between the unpaired electron of the half-filled π orbital on each radical.

These TC bands appear to superpose upon the vibrational structure of the radical cation in solution which is observed at 750–840 nm. It can be explained if we consider that the CT band in the solid is more intense than the vibrational transitions of the monomer in solution. The position of the TC band of these products varies very little except for the metoxipromazine, which has a strong band very much displaced toward the near ir region. However, a qualitative difference, not in the wavelength but in the intensity, could be found and this difference could be related to the magnetic susceptibility found for these compounds. Thus, in Fig. 2, it can be seen that the less intense CT corresponds with the lowest values of χ_m. Therefore, it can be appreciated that the intensity of these bands follows the sequence: –H > –CF$_3$ > –Cl > –OCH$_3$.

As paramagnetism decreases, the CT increases. This must be related to the influence of the different R_2 substituents upon the π structure of the nucleus and consequently upon the spin overlap of the radicals. As there seems to be a correlation of the spin-exchange coupling parameter and the intensity of the CT band (approximately proportional to the square of an overlap integral between neighbouring radicals (16)), a small change in the orientation of the radical produced by the R_2 substituents should be capable of modifying considerably the overlap integral. This produces a different intensity of the CT absorption and different values of magnetic susceptibility.

(b) Bromides. Figure 3 shows the diffuse reflectance spectra of the bromides. The reference spectrum is the same. The R.D.

spectra of these products were taken from different disks, at different time.

In these spectra two bands can be appreciated. There is one about 500–600 nm and another between 650 and 1200 nm, similar to the perchlorates. No other transitions were found up to 2500 nm. The position of the first band corresponds to the same products in solution. The other band corresponds with the CT band of the ClO$_4^-$ radical cation, at approximately the same wavelength. However, there is a splitting of this band and although it is not completely resolved, it seems to consist of two prominent peaks. The energy of the first splitting band is a little lower than the maximum of the perchlorate cation radicals CT band. Though some kind of splitting also exists in the perchlorate radicals, this is not so well resolved as in the bromides.

The magnetic susceptibilities of the bromides are much lower than the ClO$_4^-$ cation radicals. Therefore, it has to be supposed that the steric effect produced by the Br$^-$ is smaller than that produced by the ClO$_4^-$. Consequently, the interaction between the bromides is stronger. The effect produced by each R_2 substituent seems to be comparatively increased, showing in the CT band, where a clear splitting is produced. This is characteristic of strong interactions between ion radicals (17) as for example in p-phenylendiamide bromide and Wursted's bromide (18).

2. R_{10} Effect: Derivatives with $R_2 = -Cl$ and Different R_{10}

(a) ClO$_4^-$ cation radicals. Figure 4 shows the R.D. spectra of the three products. There seems to be not much difference between them. Also the χ_m of the three products are very similar. In this case the R_{10} substituents seem not to exert much influence upon the TC transition.

(b) Bromides. Figure 5 shows the respective spectra. Here there seems to be much more difference in the corresponding spec-
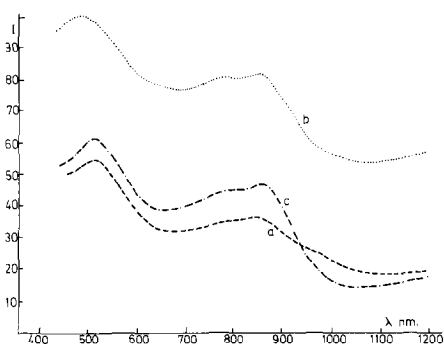
FIG. 4. Diffuse reflectance spectra of the perchlorates of derivatives with R_2 = Cl and different R_{10}: (a) chlorpromazine, (b) prochlorperazine, and (c) perfenazine.

tra. Chlorpromazine is the more intense, but the prochlorperazine shows more defined bands. Also it can be appreciated in the three products that while the first band stays at 800 nm, the second, at ≈900 nm, shows slight variations in wavelength. It can be thought that the R_{10} seems to contribute in some way to CT because of the minor steric effect exerted by the Br⁻ anion between the two cation radicals.

The stacking of the radicals in the solid state should form columns in such a way that the free unpaired π electrons of each radical should overlap among several of them forming a linear chain. However, since the location of the bands suggests the dimer-type interaction, it can be thought
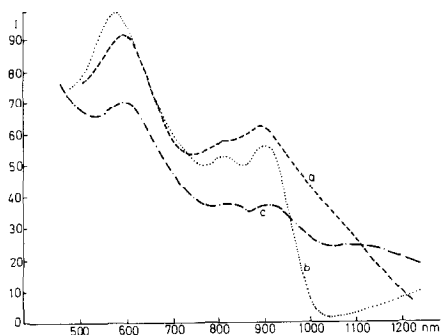
that as the R_{10} substituents are very bulky, they prevent a spread overlap, producing only interactions of the dimer type in the column (12).

If, however, the CT bands are composed of at least two peaks, as is seen in the bromides, there ought to be less steric effect exerted by the Br⁻ anion, which produces a stronger interaction between the unpaired π electrons. This suggests that the interaction can be more than the dimer type.

Summarizing the above-mentioned results, the CT interaction in these cation radical salts is largely affected by (a) the R_2 substitution, which shows a gradient of the CT band and of χ_m values depending on the electron-withdrawing or electron-donating power of the substituents upon the electronic structure of the phenothiazine nucleus. Thus, the $-OCH_3$ substituent show the strongest CT band and the lowest χ_m value (in the bromide and in the perchlorate compounds), that with $R_2 = -H$ is the compound that produces the least CT band and the higher χ_m values. The $R_2 = -CF_3$ and $-Cl$ substituents produce CT bands and χ_m values depending on the capacity of polarization of the R_2 upon the radical cation. Also the polarization of the radical cations depends on the steric effect produced by the size of the counter anions. (b) From the two counter anions studied, Br⁻ and ClO_4^-, the Br⁻ seem to produce the strongest interaction between the radicals, which are seen in the CT band by a clear splitting of the band and higher intensity of the band of minor energy, and in the χ_m values the Br are less paramagnetic than the perchlorates. This indicates a higher coupling of the free electron of the radicals. (c) The R_{10} effect shows up principally in the diffuse reflectance spectra of the bromides. This is so because as the distance between two radicals is shorter, owing to the smaller size of the Br⁻ anion, the interaction will be stronger and the steric effect produced by

FIG. 5. Diffuse reflectance spectra of bromides of derivatives with R_2 = -Cl and different R_{10}: (a) chlorpromazine, (b) prochlorperazine, (c) perfenazine.

the long and voluminous lateral chain R_{10} will be noticed. The chlorpromazine has the strongest CT band and perfenazine is the weakest of the three derivatives with R_2 = –Cl.

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