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### **Infrared Study of Seven Potential Siderophores Analogous to Salicylaldehyde Benzoyl Hydrazone (SBH)**

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**INFRARED STUDY OF SEVEN POTENTIAL SIDEROPHORES  
ANALOGOUS TO SALICYLALDEHYDE BENZOYL HYDRAZONE  
(SBH)**

**Key words :** Salicylaldehyde benzoyl hydrazone. Substituent effects. Infrared Spectroscopy.

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**ABSTRACT**

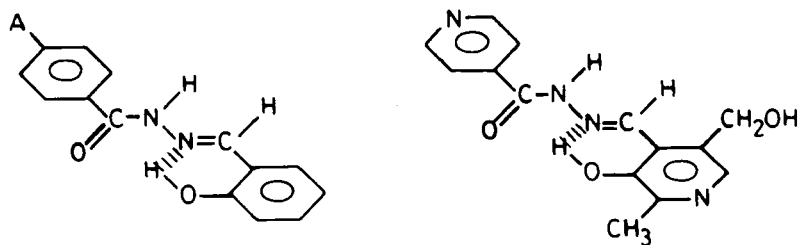
Seven siderophores which differ from salicylaldehyde benzoyl hydrazone by only one substituent on the benzoyl moiety are studied with infrared spectroscopy between 2000 and 1100  $\text{cm}^{-1}$ . The shift of the amide-I band and the intensity variations of cycle stretching bands are specially discussed according to the nature of the substituents.

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## INTRODUCTION

Increased interest aroused from salicylaldehyde benzoyl hydrazone (SBH - see figure) comes from its complexation capabilities: as neighboring aroyl hydrazones, such as pyridoxal-isonicotinoyl-hydrazone (PIH), SBH seems able to eliminate excess iron ions in living media<sup>1-8</sup>, occurring in thalassemias and other refractory anemias. It would therefore be proposed as substitute to transferrioxamine, the drug currently used for that therapy, but which reveals costly and not free from side effects.



These compounds have been studied by UV spectrometry and X-ray crystallography<sup>9-15</sup>. In recent papers, we proposed band assignments in IR spectra, for free ligands<sup>16</sup> or their complexes formed with Fe<sup>3+</sup> in solid phase, in the case of SBH, PIH, and analogous compounds<sup>17</sup>. We also specify the geometry of the most stable conformer for these compounds (see figure).

In this work, we extend the IR study for seven other ligands (detailed in table 1) bearing para substituents on the benzoyl part of the SBH skeleton.

## EXPERIMENTAL

Compounds were synthesized by Dr Ponka et al (Montreal, Canada). For this IR study, solvent was DMSO. Its use is somewhat difficult, due to its highly hygroscopic character, but it is the only one usable for the whole set of compounds, because of their weak solubility. A cell of 25  $\mu$ m path, with KBr windows was used because of the high absorption of DMSO. Solid state spectra have been recorded as KBr pellets. Spectra were run on a NICOLET 60 SX, with a 2 cm<sup>-1</sup> resolution.

TABLE 1  
Para substituent

A	NH <sub>2</sub>	OH	CH <sub>3</sub> O	(CH <sub>3</sub> ) <sub>3</sub> C	H(SBH)	F	Cl	Br
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with A-R : A -  $\Phi$  - CO - NH - N = CH -  $\Phi$  - OH (fig.)

IR study was generally restricted within the range 2500-1200  $\text{cm}^{-1}$ . Broad bands due to dimeric or polymeric associations hamper examination in the 3000  $\text{cm}^{-1}$  area, and below 1200  $\text{cm}^{-1}$  a great number of medium or weak bands makes assignments difficult.

## RESULTS

After studying the main bands for the diverse investigated ligands, we will present results relative to ring- or substituent- characteristic vibrations.

### 1) Assignment of Main Bands

Wave numbers and relative intensities are gathered in table 2 (DMSO solution) and 2' (solid state, KBr pellet). In the table, molecules are (roughly) ordered according to the electron-donor (or -acceptor) character of the substituent.

Assignments proposed for the main bands of SBH <sup>16</sup>, i.e. amide I, amide II, amide III and ( $\nu_{\text{CO}} + \delta_{\text{OH}}$ ) bands, are used as a basis for the other investigated molecules. As we already noticed, the unexpected position of the amide III band ( $\nu_{\text{CN}}$  for main contribution) can be explained by the high conjugation exhibited in this series of molecules <sup>16</sup>.

In solution, the amide I band is the only band exhibiting significant substituent shifts (16  $\text{cm}^{-1}$  variation range). The band frequency decreases with increasing donor character of the para substituent, as evidenced by the first three entries in table 2 (NH<sub>2</sub>, OH, OCH<sub>3</sub> substituents). Such variations are in agreement with literature <sup>18,19</sup>: an electron-donating substituent lowers the polarity of the CO group, the main contribution of the amide I band, and therefore lowers the stretching frequency. Observing so large substituent-induced variations

TABLE 2

Assignments, Wave Numbers ( $\text{cm}^{-1}$ ) and Relative Intensities in Solution (DMSO)

Substituent	Assignments			
	Amide I	Amide II	Amide III	$\nu_{\text{CO}+\delta\text{OH}}$
NH <sub>2</sub>	1661 m	1551 mw	1356 w	1279 s
OH	1668 s	1557 m	1357 m	1278 vs
OCH <sub>3</sub>	1669 s	1558 mw	1357 w	1283 s
C(CH <sub>3</sub> ) <sub>3</sub>	1672 s	1555 m	1359 m	1281 s
H (SBH)	1673 s	1554 m	1357 m	1283 s
Cl	1676 vs	1558 m	1358 w	1287 s
Br	1674 s	1559 m	1358 mw	1284 s
F	1677 s	1556 m	1359 m	1290 s

vs : very strong s : strong m : medium w : weak mw : medium weak

TABLE 2'

Assignments, Wave Numbers ( $\text{cm}^{-1}$ ) and Relative Intensities in Solid State (KBr)

Substituent	Assignments			
	Amide I	Amide II	Amide III	$\nu_{\text{CO}+\delta\text{OH}}$
NH <sub>2</sub>	1659 m	1544 m	1358 m	1279 s
OH	1637 m	1550 s	1363 m	1283 s
OCH <sub>3</sub>	1623 m	1572 m	1375 m	1306 s
C(CH <sub>3</sub> ) <sub>3</sub>	1646 s	1558 m	1365 m	1288 s
H (SBH)	1674 s	1540 m	1356 m	1274 s
Cl	1653 m	1567 m	1369 m	1291 m
Br	1652 m	1561 m	1369 m	1289 m
F	1646 s	1560 m	1360 w	1294 m

s : strong m : medium w : weak

on the carbonyl frequency, due to para substitution, implies a good transmission along the aromatic ring and the ring-carbonyl bond. This would require that part of the molecule to be nearly coplanar, a conclusion we already proposed from an IR study of SBH <sup>16</sup>, recently confirmed by crystallographic studies <sup>20</sup>.

More puzzling are the results obtained with KBr pellets. Large frequencies variations (by respect to solution spectra) are observed, but remain up to now difficult to rationalize. Presumably, these variations correspond to the formation of dimeric or polymeric species. So it was already quoted <sup>16</sup> that the amide I band may exhibit important modifications, due to its high sensibility to the existence of associated forms <sup>18</sup>. The OCH<sub>3</sub> substituted derivative deserves special attention. Indeed, for that compound, differences between solution and solid phase spectra are definitely more important than for other compounds. Since its behavior in solution is quite comparable to other derivatives, it seems likely that this compound is strongly associated in the solid phase.

## 2) Ring and Substituent Specific Vibrations

The investigated molecules possess two different aromatic parts: a phenyl ring (with a carbonyl group and para substituent), and a phenolic ring, ortho-substituted by an imine group.

### *2-a) Bands attributed to ring vibrations*

As stated in literature <sup>18,19</sup>, aromatic cycles exhibit two types of characteristic C-C stretching vibrations: a quadrant mode (near 1600 cm<sup>-1</sup>) and a sextant mode (between 1400-1500 cm<sup>-1</sup>). Unless symmetry restrictions, each type leads to two frequencies, with differing sensitivity to electronic effects of substituents.

For ortho-substituted cycle, four bands are expected: between 1620-1585 cm<sup>-1</sup>, 1590-1565 cm<sup>-1</sup>, 1510-1470 cm<sup>-1</sup> and 1465-1430 cm<sup>-1</sup>.

The second band may be enhanced by conjugation. The intensity of the third band is strong, in case of electron-donor substituents.

The four bands expected for a para-substituted ring are located between 1620-1585 cm<sup>-1</sup>, 1590-1565 cm<sup>-1</sup>, 1525-1480 cm<sup>-1</sup> and 1420-1400 cm<sup>-1</sup>. Intensities of the first two bands are directly related to the perturbations of electron density within the aromatic cycle: the more important the difference of

electronic effects between para substituents (inductive or mesomeric) is, the more intense result the bands. However, the second band generally remains weak, except in cases of conjugation or when the substituent is an halogen. Intensity of the third band increases for electron-donating substituents, but can vanish for electron-withdrawing groups. The fourth band is weak.

Experimental results (see tables 3 and 3') are in good agreement with the preceding literature observations. However, over the eight expected bands, only six are observed since the overlap of their spectral ranges only allows for identifying the more intense components.

Depending on the intensities and wave numbers of the differing bands we assign them (whenever possible) to an ortho-substituted cycle (salicylaldehyde fragment) or to a para-substituted ring (benzoyl fragment), respectively quoted as O or P in the tables.

Intensity variations of the first band (near  $1600\text{ cm}^{-1}$ ) allow for verifying substituent influences. For groups with electron-donating mesomeric effects ( $\text{NH}_2$ , OH,  $\text{OCH}_3$ ), whereas the other substituent (the carbonyl group) is electron withdrawing, the  $1600\text{ cm}^{-1}$  band is strong. With a t-butyl group (where only inductive effect intervenes), a medium-intensity band results. At last, halogeno-substituents, although their mesomeric electron-donating effect is opposite to that of the carbonyl group, exhibit, due to electronegativity, an electron-withdrawing inductive effect. This can explain the medium-intensity band at  $1600\text{ cm}^{-1}$  for the halogeno substituted compounds.

The band near  $1580\text{ cm}^{-1}$  generally remains of low intensity. Its assignment to either one or the other of the two cycles seems difficult. In solid phase, its intensity increases (from weak to medium) as well with an electron-donating group (OH) as with a fluoro substituent. For these two spectral ranges, bands from the two cycles overlap, and only the more intense one can be identified.

By contrast, differing spectral ranges for the last two bands allow for an unambiguous assignment. The third band, missing in SBH, can be safely attributed to the para-substituted part. Conversely, for similar reasons, the  $1480\text{ cm}^{-1}$  band is associated with the ortho-substituted fragment.

It is to be noticed that, by difference with the amide I or ( $\nu_{\text{CO}} + \delta_{\text{OH}}$ ) bands, the massif of these aromatic bands are particularly not sensitive to phase changes (from solution to solid).

TABLE 3

Wave Numbers ( $\text{cm}^{-1}$ ) and Relative Intensities of Rings Bands in solution (DMSO)

A	Assignments					
	P*O	P*O***	P**	O**	O	P
NH <sub>2</sub>	1607 s	1562 w	1516 m	1490 m	1455 w	-
OH	1606 s	1590 w	1513 m	1490 m	1455 w	-
OCH <sub>3</sub>	1606 s	1576 vw	1511 m	1490 m	1457 w	-
C(CH <sub>3</sub> ) <sub>3</sub>	1610 m	1567 sh	1507 w	1490 m	-	1400 w
H (SBH)	1606 m	1582 w	-	1490 m	1456 w	-
Cl	1606 m	1568 sh	1476 w	1490 mw	1457 mw	-
Br	1606 mw	1573 sh	1473 w	1490 m	1457 mw	-
F	1606 m	1587 m	-	1487 m	1456 w	1434 w

s : strong m : medium w : weak sh : shoulder vw : very weak mw : medium weak P : para cycle O : ortho cycle

\* enhanced for different electronic effects \*\* enhanced for donor substituent \*\*\* enhanced by conjugation

TABLE 3'

Wave Numbers ( $\text{cm}^{-1}$ ) and Relative Intensities of Rings Bands in Solid State (KBr)

A	Assignments					
	P*O	P*O***	P**	O**	O	P
NH <sub>2</sub>	1602 s	1570 w	1514 m	1493 m	-	1409 w
OH	1607 s	1585 m	1512 m	1492 m	-	-
OCH <sub>3</sub>	1604 m	1583 w	1508 m	1487 m	1463 w	1417 w
(CH <sub>3</sub> ) <sub>3</sub>	1608 m	-	1512 w	1488 m	1463 w	1406 w
H (SBH)	1606 m	1579 w		1488 m	1445 w	1415 vw
Cl	1608 m	-	1473 vw	1487 m	1464 w	1423 w
Br	1608 m	1571 w	1475 w	1487 m	1465 w	1419 w
F	1611 m	1588 m	-	1484 m	1443 mw	1411 vw

s : strong m : medium w : weak mw : medium-weak vw : very weak P : para cycle O : ortho cycle

\* enhanced for different electronic effects \*\* enhanced for donor substituent \*\*\* enhanced by conjugation



TABLE 4  
Bibliographic Results <sup>18</sup>

Substituent	Wave numbers (cm <sup>-1</sup> )	
Ar-NH <sub>2</sub>	1638-1602 (NH <sub>2</sub> scis.), s	1330-1260 (ν <sub>aryl-N</sub> ),s
Ar-OH	1410-1310 (δ <sub>OH</sub> ),m	1260-1180 (ν <sub>CO</sub> ),s
Ar-O-CH <sub>3</sub>	1470-1435 (O-CH <sub>3</sub> ),m	1310-1210 (aryl-O),vs
Ar-C (CH <sub>3</sub> ) <sub>3</sub>	1395-1385	1373-1365
Ar-F	1270-1100 (ν <sub>CF+ring</sub> ),m	

s : strong m : medium vs : very strong

TABLE 5  
Experimental Results for Substituent Bands

Substituent	Wave numbers (cm <sup>-1</sup> )	
	solution (DMSO)	solid (KBr)
Ar-NH <sub>2</sub>	-	1627 m
Ar-OH	1244 m	1237 m
Ar-OCH <sub>3</sub> (O-CH <sub>3</sub> )	-	1454 w
(CH <sub>3</sub> )	-	1375 m
(aryl-O)	1255 vs	1262 s

s : strong m : medium vs : very strong w : weak

## 2-b) Miscellaneous results

Table 4 gathers literature information about characteristic substituent frequencies (within the spectral range under scrutiny) and table 5 details the observed bands.

The more puzzling results come from the methoxy-substituted compound: an important difference is observed with SBH, since (apart from changes due to modification in the aromatic cycles) bands near 1255 cm<sup>-1</sup> (table 5) are the most intense in the spectrum. Studying this molecule in CH<sub>3</sub>OD, indicates that the 1255 cm<sup>-1</sup> band is not very sensitive to deuteration (in contrast with bands

attributed to  $\nu_{\text{CO}}+\delta_{\text{OH}}$ , located in the same range), the result is in agreement with the proposed assignment (aryl-O band).

Generally other substituents lead to weak or to medium intensity bands. And even, no specific band can be safely attributed to the t-butyl group.

## CONCLUSION

For the seven investigated siderophores, band assignments indicate:

- an homogeneous behavior of frequencies and intensities for amide and  $\nu_{\text{CO}}+\delta_{\text{OH}}$  bands

- a lowering of the amide I band with increasing electron-donating character of the para-substituent on the phenyl ring. This is consistent with a nearly coplanar geometry for that fragment of the molecules

- varying intensities for the C-C skeletal vibrations of the cycles (quadrant and sextant modes), depending on the electronic effect of the substituents.

This last point seems particularly interesting since the observation of intense bands in the ring-vibration range has been often attributed to a stretching C-N band <sup>14</sup>, or, for complex formation, to associated-amide bands <sup>21,22</sup>. According to the present study, another interpretation could be suggested: *enhancement of cycle-vibrations* due to electronic effects (for instance, possibly traducing, in cases of complex formation, influence of the metal ion on the cycle). This point is currently under study <sup>23</sup>.

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