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HETEROCYCLIC THIOAMIDES PAIRING THROUGH SELECTIVE HYDROGEN BONDING.

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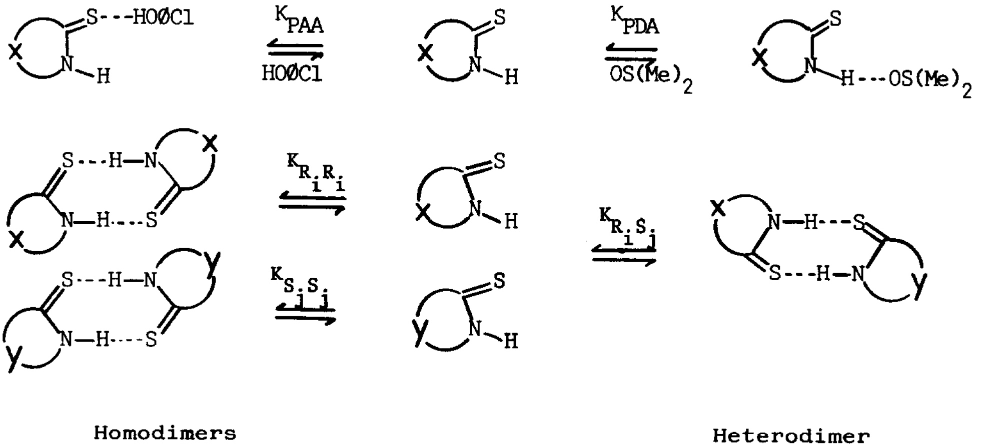
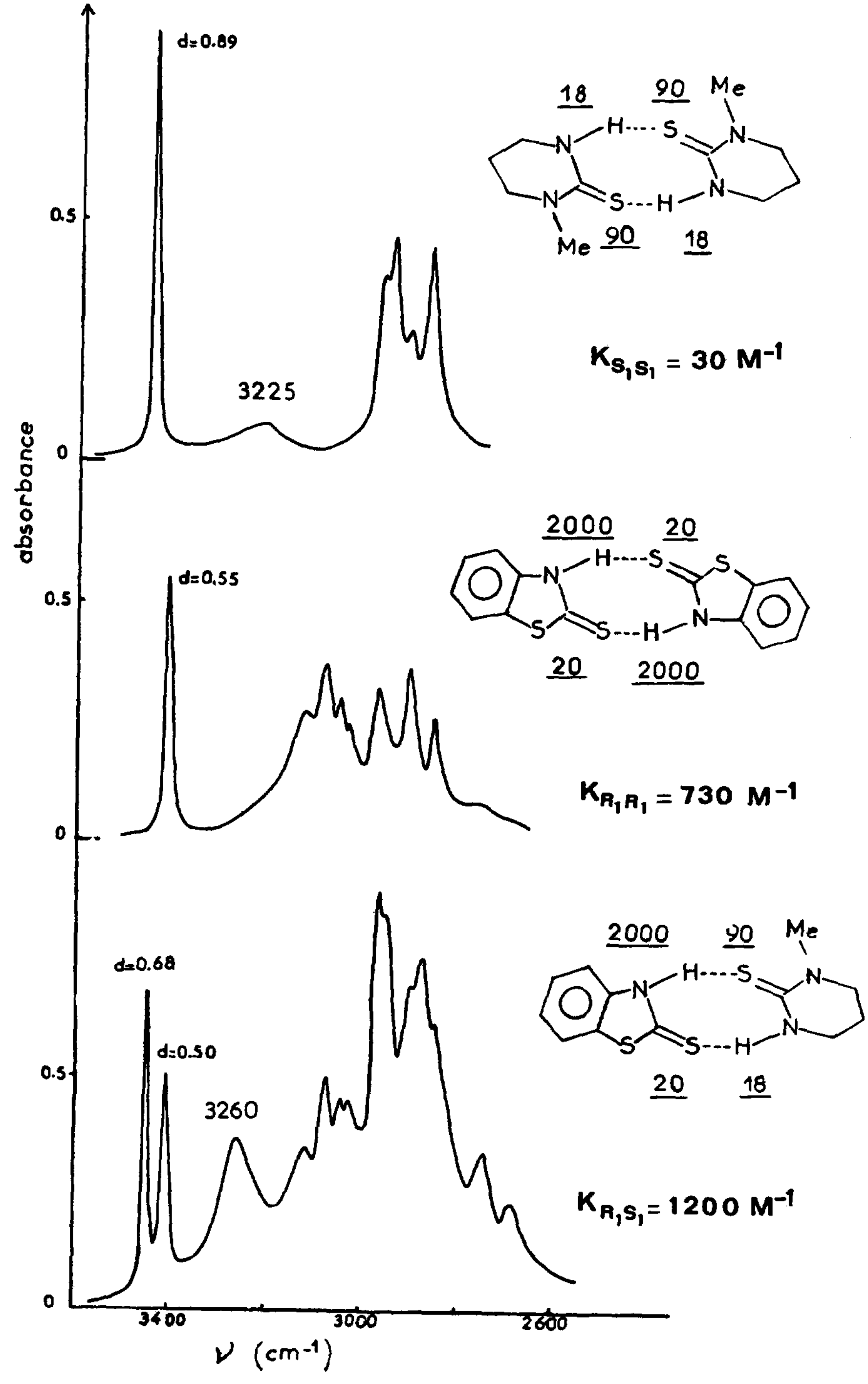
Compared to the number of studies on the selective hydrogen bonding of nucleotide bases[1], no quantitative results have yet been reported for selective hydrogen bonding in much more simple models such as heterocyclic thioamides R_i, S_j.

In a study of bifunctional catalyst design, we have already reported[2] their homoassociation constants ($K_{R_iR_i}$ and $K_{S_jS_j}$), and their hydrogen bonding tendencies respectively towards DMSO (K_{PDA}) and p-ClC_6H_4OH (K_{PAA}) in CCl_4 by i.r. spectroscopy. The structural changes of X or Y specifically affect the proton donating ability of the N-H proton and the proton accepting ability of the C=S sulphur atom.



We wish to report that selected pairs of heterocyclic bases, one with a high proton donating ability (large K_{PDA}) and the other with a high proton accepting ability (large K_{PAA}) can be involved in heteroassociated species of larger stability than the homoassociated species of the parent compounds.

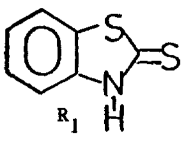

absorbance
d=0.89
0.5
0
3225
18
90
Me
N
H
S
90
18
$K_{S_1S_1}$ = 30 M^{-1}
d=0.55
0.5
0
2000
20
20
2000
$K_{R_1R_1}$ = 730 M^{-1}
d=0.68
d=0.50
0.5
0
3260
2000
90
Me
20
18
$K_{R_1S_1}$ = 1200 M^{-1}
3400
3000
2600
ν (cm^{-1})

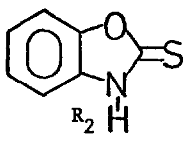
Experimental evidence for heteroassociated species: The figure shows the i.r. spectra in CCl_4 (2600-3500 cm^{-1}) of pure 1-Me-tetrahydropyrimidine-2-thione S_1 (C_S =1.5 10^{-3} M), of pure benzothiazoline-2-thione R_1 (C_R=1.5 10^{-3}M) and of a mixture 1:1 of R_1 and S_1 (C_R=C_S=1.5 10^{-3}M). The spectra of R_1 and S_1 exhibit respectively the free N-H absorptions (3409 for R_1 and 3450 for S_1) together with the associated N-H bond (3225 for S_1 and c.a. 3000 for R_1)[3]. The i.r. spectra of the mixture R_1S_1 shows a decrease of both the two free N-H absorptions, a large increase in the absorption below 3000 cm^{-1} and the appearance of an intense absorption at 3260 cm^{-1}. This behaviour is well accounted for by a decrease of both monomeric forms due to the occurence of a new heteroassociated pair R_1S_1.[4]

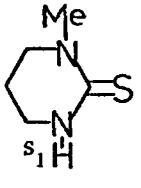
In this heteroassociated pair, the absorption at c.a.3000 cm^{-1} involves a strong hydrogen bond between the two centers of large hydrogen bonding tendencies: the C=S sulphur atom of S_1 (K_{PAA} = 90 M^{-1}) and the N-H proton of R_1 (K_{PDA}=2000 M^{-1} The occurence of a cyclic dimer in the heteroassociated pair instead of a possible linear dimer is clearly shown by the absorption at 3260 cm^{-1}. This high frequency indicates that the hydrogen bond occurs between two centers of low hydrogen bonding tendencies (C=S sulphur atom of R_1: K_{PAA} = 20 M^{-1}; N-H of S_1:K_{PDA}=18 M^{-1}); furthermore its high intensity indicates that this bond is formed to a large extent. The occurence of such a cyclic dimer can be rationalized by a minimisation of the dipole moment in the heteroassociated pair in CCl_4.

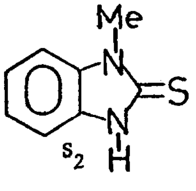
TABLE

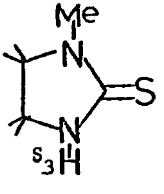
Compounds	K_{PDA}(DMSO)	K_{PAA}(p-ClC_6H_4OH)	$K_{R_iR_i}$ or $K_{S_jS_j}$	$K_{R_1S_j}$	$K_{R_2S_j}$
R_1	2000	20	730	-	-
R_2	3000	25	620	-	-
S_1	18	90	30	1200	1500
S_2	400	50	340	1050	1200
S_3	42	120	100	1200	2000
S_4	300	245	2250	5400	7500

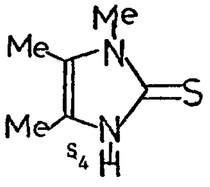

R_1


R_2


S_1


S_2


S_3


S_4

The calculated value of the heteroassociation constant according to eq. I[5]is larger than both the homoassociation constants for R_1R_1 and S_1S_1 pairs. The table reports selected values of heterocyclic thioamides pairing. The chosen thioamides have crossed proton donating and proton accepting abilities; when this crossing is not respected, the heteroassociation constant is found between the two homoassociation constants. Thus, when 2-thiopyridone (K_{PDA}= 450 M^{-1},K_{PAA}=260 M^{-1},K_{RR}= 6000 M^{-1}) is mixed with S_3, the heteroassociation constant is 1100 M^{-1}.

In summary, the preliminary results presented here show that heterocyclic thioamides can be involved in base pairing as do the nucleotide bases. Some applications of this selective pairing in reactivity and in physical extraction are in progress.

References and notes.

[1]a) "Molecular Associations in Biology", B. Pullman Ed. Academic Press, N.Y. 1968.
b) Y. Kyogoku, B.S. Yu, R.C. Lord and A. Rich, Jerusalem Symp. on Quantum Chem. and Biochemistry, IV, 1972, 223.
c) V.L. Antonovsky, A.S. Gukovskaja, G.V. Nekrasova, B.I. Sukhorukov and I.I. Tchervin, Biochimica and Biophysica Acta, 1973, 331, 9-20.

[2]a) E. Gentric, J. Lauransan, C. Roussel and J. Metzger, J. Chem. Soc. P II, 1976; 565.
b) ibid. under press paper 6/1107.

[3] Association constants $K_{R_iR_i}$, $K_{S_jS_j}$ are extracted as given in 2a.

[4] As an example, the concentrations in the various species at equilibrium, calculated with $K_{R1S1} = 1200\ M^{-1}$, are:

Concentration	R_1	R_1R_1	S_1	S_1S_1	R_1S_1
Pure R_1	$7.3\ 10^{-4}$	$3.9\ 10^{-4}$	-	-	-
Pure S_1	-	-	$1.4\ 10^{-3}$	$5.6\ 10^{-5}$	-
$R_1 + S_1$	$5.5\ 10^{-4}$	$2.2\ 10^{-4}$	$9.0\ 10^{-4}$	$1.5\ 10^{-5}$	$5.0\ 10^{-4}$

One observes a larger decrease in the dimer concentrations than in the monomer concentrations.

[5] Heteroassociation constants are evaluated from equation I ($K_{R_iS_j}$):

$$K_{R_iS_j} = \frac{1}{B_{R_i}B_{S_j}} \frac{(1-\alpha\beta)^2}{(d_{R_i} - \beta d_{S_j})(d_{S_j} - \alpha d_{R_i})} \left[C^o_{R_i} - B_{R_i}\frac{d_{R_i} - \beta d_{S_j}}{1-\alpha\beta} - A_{R_i}\left(\frac{d_{R_i} - \beta d_{S_j}}{1-\alpha\beta}\right)^2 \right]$$

A_{R_i} and B_{R_i} are obtained by statistical treatment of the experimental curve $C^o_{R\,i} = f(d)$ according to $C^o_{Ri} = A_{Ri}d^2 + B_{Ri}d$ in the study of the homoassociation of pure R_i.(see 2a). $K_{R_iR_i} = A_{Ri}/\ 2B^2_{Ri}$, $_{Ri} = 1/B_{Ri}$.

d_{R_i} and d_{S_j} are the absorbances at the corresponding free N-H frequencies. C^o_{Ri} is the formal concentration in R_i . α and β are coefficients to account for the overlapping of the free N-H frequencies. In the given figure, α equals 0.042 and β equals 0.045.

The random errors calculated from statistical analysis (C.A. Bennett and N.L. Franklin, " Statistical Analysis in Chemistry and the Chemical Industry", Wiley, New-York, 1954, p. 228) on coefficients A_{Ri} and B_{Ri} (0.95 confidence level) lead to a calculated error on K_{RiSj} of c.a. 40 %. However, repetition of experiments shows that these errors are largely overestimated (20 %).

All the experiments were performed at 25°C.