Studies on Azole-to-Azole Interconversion − An Interesting Case of Absence of a "Primary Steric Effect" in the Ring-Degenerate Equilibration between *ortho*-Substituted 3-Aroylamino-5-methyl-1,2,4-oxadiazoles and 3-Acetylamino-5-aryl-1,2,4-oxadiazoles in Methanol

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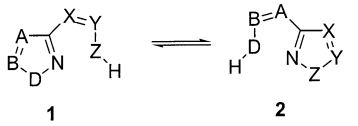
The title reaction has been studied by ^{1}H NMR, both in CD_3OD and in *t*BuOK/CD_3OD. The components of the electronic effect of the substituent on the benzene ring show different contributions depending on whether the equilibrium between neutral (strong prevalence of the "proximity polar effect") or anionic species (balance between "ordinary and proximity polar effects") is considered. The "primary steric effect" does not significantly affect the reactivity, probably because of the importance of the internal amidic conjugation. For the *ortho*-methoxy derivative, interesting "special" proximity effects have been observed.

Introduction

The Boulton, Katritzky, and Majid-Hamid scheme,[1a] a monocyclic rearrangement of heterocycles in which an unsaturated side chain is involved (see Scheme 1), represents an interesting pathway for the synthesis of five-membered nitrogen aromatic heterocycles.[1] Its scope has been enlarged by Korbonits and co-workers,[2] who pointed out that in 1,2,4-oxadiazoles a ring−ring interconversion into five-membered nitrogen dihydroheterocycles (e.g., pyrazolines) could also occur in the presence of saturated side chains.



Scheme 1

In some instances the classic monocyclic rearrangement of heterocycles is reversible,[1,3] as may occur when, for example, an O−N bond is both cleaved and formed (i.e., in **1** and **2**: Z = D = O). Of course, the thermodynamic requirement is that the starting and final products have similar stabilities.

Examples of potentially reversible ring interconversions are collected in Scheme 2; it has been observed, for example, that:

- as expected, the (*Z*)-oximes of 3-acyl-1,2,4-oxadiazoles (**3**) rearrange irreversibly[4] into the corresponding 3-acylamino-1,2,5-oxadiazoles (**4**), the higher stability of which essentially depends both on the greater aromaticity of 1,2,5-oxadiazole (Bird's I_5 index:[5] 43) with respect to 1,2,4-oxadiazole (Bird's I_5 index: 39) and on the effective resonance within the amido group;
- in contrast, an equilibrium, also dependent on the nature of R, occurs[6] between 3-(*o*-hydroxyphenyl)-1,2,4-oxadiazoles (**5**) and 3-acylaminobenzisoxazoles (**6**): this is because **5** is favoured by the diaryloid effect[3a] and by the strong hydroxy−aryl interaction (especially important in the relevant anion), while the resonance within the amido group effectively contributes to the stability of **6**, in which on the other hand, the resonance of isoxazole (Bird's I_5 index: 47) is strongly reduced because of the benzocondensation;
- 3-acetylamino-5-methylisoxazole (**7**) could not be converted[7] into 3-acetonyl-5-methyl-1,2,4-oxadiazole (**8**), as was to be expected on the grounds of the higher aromaticity of **7**, the stability of which is furthermore increased by the amide resonance.

Of special interest are cases in which starting and final ring are identical: a ring-degenerate interconversion then

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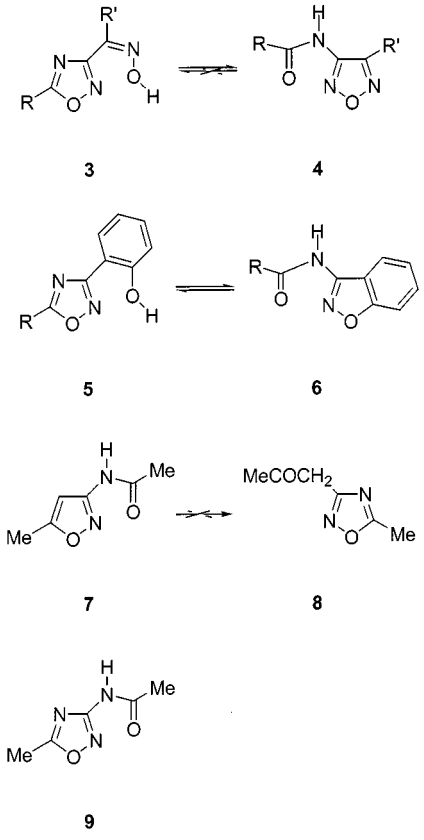


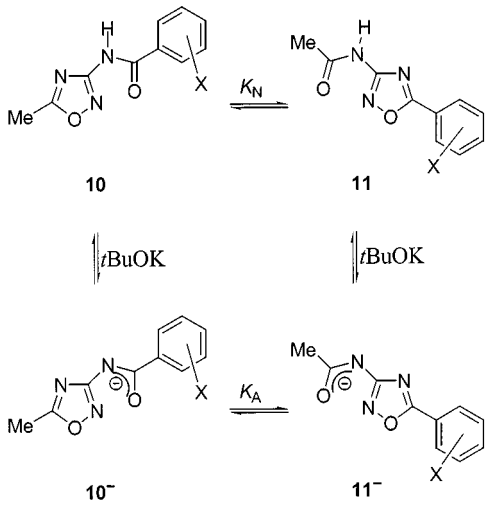
Scheme 2

occurs and can in turn be reversible, as we pointed out when reporting some examples in the 1,2,4-oxadiazole series.[3a−3e]

We studied the fully degenerate rearrangement of the anion of 3-acetylamino-5-methyl-1,2,4-oxadiazole (**9**) in DMSO[3b] and the quasi-fully degenerate rearrangement of **9** with a trideuterated acetyl group in the same solvent.[3c] Semiempirical[3c] and ab initio[3e,8] calculations have been also reported. The ring-degenerate equilibrium between some *meta*- or *para*-substituted 3-aroylamino-5-methyl-1,2,4-oxadiazoles (**10**) and the corresponding 3-acetylamino-5-aryl-1,2,4-oxadiazoles (**11**) both in CD_3OD and in *t*BuOK/CD_3OD (Scheme 3) has also been examined.[3d]

The measured equilibrium constants for the **10/11** couple were found to be quite differently favoured by electron-repelling substituents depending on whether neutral or anionic forms were involved;[3d] the smaller substituent effect in the first case ($\rho_m = -0.62$ and $\rho_p = -0.37$) in comparison with that in the second one ($\rho_m = -1.95$ and $\rho_p = -1.52$) was convincingly interpreted on the grounds of the electronic effects at play (e.g. internal carboxamide resonance, aryl−carbonyl resonance,[9] amidic nitrogen atom/1,2,4-oxadiazol-3-yl interaction, diaryloid effect[3a]).

In this paper we extend the study of the equilibration of the **10/11** couples to the case of *ortho*-substituted derivatives (X = H, MeO, Me, Cl, Br, CF_3, NO_2).



Scheme 3

Results and Discussion

Equilibration Reaction

Methanolic solutions of **10** or **11**, either as such or converted into their conjugate bases by addition of *t*BuOK, were kept at 313 K until analytical (^{1}H NMR) determinations gave constant mixture compositions (Table 1). Significantly enough, while **11** had been found to prevail completely in the neutral equilibration of both *meta*- (K_N = 3.6−10.1) and *para*-substituted (K_N = 5.3−13.3) derivatives,[3d] the electron-withdrawing *ortho* substituents significantly shifted the equilibrium composition towards **10**, which became the main component ($K_N < 1$) for X = *o*-CF_3 and *o*-NO_2 (Table 1).

Table 1. Equilibrium constants and relevant compositions (%) for the rearrangement **10a−r** ⇌ **11a−r** at 313.15 K

X	In CD_3OD [**10**]/[**11**][a]	K_N	In CD_3OD/*t*BuOK [**10**$^-$]/[**11**$^-$]	K_A
a: *p*-MeO	7:93	13.3	22:78	3.55
b: *p*-Me	8:92	11.5	30:70	2.33
c: H	9:91	10.1	38:62	1.63
d: *p*-Cl	11:89	8.09	67:33	0.493
e: *p*-F_3C	14:86	6.14		
f: *p*-NC	15:85	5.67	90:10	0.111
g: *p*-O_2N	16:84	5.25	92:8	0.087
h: *m*-OMe	11:89	8.09	41:59	1.44
i: *m*-Me	9:91	10.1	32:68	2.13
j: *m*-Cl	16:84	5.25	78:22	0.282
k: *m*-F_3C	17:83	4.88		
l: *m*-O_2N	22:78	3.55	93:7	0.0753
m: *o*-MeO	42:58	1.38	24:76	3.17
n: *o*-Me	7:93	13.3	26:74	2.85
o: *o*-Cl	44:56	1.27	90:10	0.11
p: *o*-Br	43:57	1.32	93:7	0.075
q: *o*-F_3C	58:42	0.72	95:5	0.053
r: *o*-O_2N	78:22	0.28	100:0	

[a] Data concerning **10a−l/11a−l** couples from ref.[3d]

As far as the conjugate bases are concerned, effective negative charge stabilisation is responsible for the great prevalence of **10**$^-$ ($K_A < 1$) observed[3d] in the presence of electron-withdrawing *meta* and *para* substituents (Table 1). Similarly to what has been observed under neutral conditions, electron-withdrawing *ortho* substituents here dictate a further shift of the equilibrium composition towards the aroylamino system. Thus, practically, only **10**$^-$ can be observed at equilibrium for X = NO_2 and, accordingly, the relevant K_A value has not been included in the free energy correlations below.

Free Energy Treatment of Equilibrium Data

A) A Hammett Equation Approach

We first attempted a simple Hammett treatment of our data. Thus, in − for example − equilibration between neutral species, we observed only a rough correlation ($n = 7$, $r = 0.7$, $\rho_o = -1.2\pm0.5$, $i = -0.5\pm0.2$). A glance at the plot as well as, on a more proper statistical basis, a calculation of residuals, in particular clearly showed the failure of the *ortho*-methoxy group to line up with the other substituents; on exclusion of the relevant point the correlation improved significantly ($n = 6$, $r = 0.937$, $\rho_o = -1.98\pm0.37$, $i = -0.15\pm0.15$), exhibiting a susceptibility constant more than one order of magnitude higher than that observed with *para* substituents (compare $\rho_p = -0.37$[3d] with $\rho_o = -1.98$). Such an extraordinary enhancement of the effect of *ortho* substituents in comparison with *para* substituents induced us to make use of a more specific approach that would be able to account more properly for the very special effects (proximity polar as well as steric) played by *ortho* substituents on kinetic and thermodynamic data.

B) An Approach by Use of the Fujita−Nishioka Equation

Several approaches can be used to discuss the effect of an *ortho* substituent on kinetic or thermodynamic data. In an elaboration of Charton's[10] primary hypothesis of dissecting the total *ortho* substituent effect into its inductive, mesomeric and steric components, Fujita and Nishioka suggested[11] the treatment of data as a sum of three contributions [Equation (1)]: the "ordinary polar effect" (assumed to be equivalent to that of a *para* substituent and expressed by, for example, the σ_p constant), the "proximity polar effect" (represented by the Swain−Lupton constant, F)[12] and the "primary steric effect" (symbolised by the Taft constant E_s).[13]

$$\log K_o/K_H = \rho\sigma_o + \delta E_s + fF_o + i \quad (1)$$

Interestingly, this treatment allows data to be combined for *ortho* and *para* substituents; *meta* substituents may also be included only when *meta* and *para* derivatives fit the same relationship. In the present instance, this condition is not met,[3d] and Equation (2) should be used.

$$\log K_{o,p}/K_H = \rho\sigma_{o,p} + \delta E_s + fF_o + i \quad (2)$$

Of course, this treatment does not take account of hydrogen bonding or of other intramolecular interactions in which an *ortho* substituent might engage, and which could therefore significantly affect the reactivity of *ortho*-substituted derivatives.

The basis of the use of multiparameter treatments is the statistical observation that the various parameters of interest show a low degree of interrelationship. Actually, a purposely carried out check revealed that a significant correlation ($r^2 = 0.687$) existed only between σ and the steric parameter E_s; in the other instances lower r^2 values (0.58 and 0.15) were calculated. As the steric parameter has been excluded from the correlation [see discussion and Equation (3) below], the multiparameter treatment can confidently be used.

Thus, by application of Equations (1) and (2) to the interconversions studied both in neutral and anionic form, the results listed in Entries 2, 3, 8, and 9 of Table 2 were obtained, displaying, at first glance, the existence of a small and a large contribution from the "primary steric" and the "proximity polar" parameters, respectively.

Anyway, the correlation coefficients (R) were no more than acceptable, and a calculation of residuals again showed that the *ortho*-methoxy group did not line up with the other substituents; thus, with the relevant point excluded, the correlation coefficients improved from 0.967−0.986 to 0.995−0.997 (compare Entries 2, 3, 8, and 9 with Entries 4, 5, 10, and 11 in Table 2), clearly indicating the occurrence of some special effect for this substituent (see below).

A close correspondence was observed between the ρ values calculated for the *para*-substituted amides (**10a−g**/**11a−g** couples; Entries 1 and 7 of Table 2) and for all *ortho*- and *para*-substituted amides (**10a−g**,**n−r**/**11a−g**,**n−r** couples: compare Entries 1 and 7 with Enries 5 and 11 of Table 2), indicating that data for *ortho* and *para* derivatives can confidently be treated in terms of a unique multiparameter free energy relationship. The values of the susceptibility constants indicated a large contribution from the "proximity polar effect", especially in neutral solution [compare $(\rho_{o,p})_N = -0.39$ and $(\rho_{o,p})_A = -1.50$ with $(f)_N = -1.70$ and $(f)_A = -2.08$]. Thus, while electron-withdrawing groups caused a shift towards **10** (or **10**$^-$) from both the *ortho* and the *para* positions, the effect in *ortho*-substituted derivatives was evidently larger because of the occurrence of a strong "proximity polar effect" that cooperated with an "ordinary polar effect" common to both sets of substituents.

As mentioned above, the "primary steric effect" does not significantly affect the thermodynamic values either of the neutral or of the anionic equilibration, as the calculated δ values show uncertainties comparable to their absolute values (0.07±0.04 and 0.06±0.04). Accordingly, fitting of data to Equation (3) similarly provides excellent correlations (Entries 6 and 12 of Table 2: $R \geq 0.993$), with only minor, if any, variations in the susceptibility constants for the polar effects [$(\rho_{o,p})_A = -0.38$ and $(\rho_{o,p})_A = -1.50$; $(f)_N = -1.96$ and $(f)_A = -1.90$].

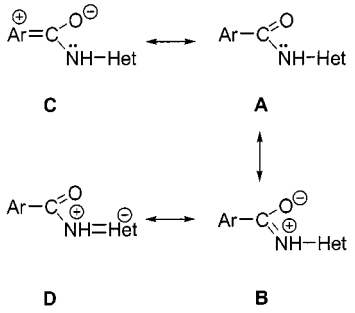
Table 2. Free energy relationships for the equilibrium between **10a−g,m−r/11a−g,m−r** couples at 313.15 K in methanol

Entry	Equation used[a]	$\rho \pm s_\rho$	$\delta \pm s_\delta$	$f \pm s_f$	$i \pm s_i$	R	n	Substituents
1	$\log (K_N)_X/(K_N)_H = \rho\sigma_p$	−0.37±0.02			0.00±0.01	0.996	7	**a−g**
2	(1)	0.32±0.46	0.13±0.16	−2.37±0.52	−0.07±0.20	0.972	7	**c**, **m−r**
3	(2)	−0.19±0.13	0.03±0.09	−2.10±0.40	−0.05±0.06	0.967	13	**a−g**, **m−r**
4	(1)	−0.54±0.45	0.06±0.10	−1.60±0.50	−0.01±0.10	0.993	6	**c**, **n−r**
5	(2)	−0.39±0.05	0.07±0.04	−1.70±0.10	0.01±0.03	0.995	12	**a−g**, **n−r**
6	(3)	−0.38±0.06		−1.96±0.10	0.00±0.02	0.993	12	**a−g**, **n−r**
7	$\log (K_A)_X/(K_A)_H = \rho\sigma_p$	−1.52±0.07			−0.08±0.03	0.996	6	**a−g**
8	(1)	−2.09±0.50	−0.07±0.20	−1.62±0.59	−0.07±0.21	0.986	6	**c**, **m−q**
9	(2)	−1.64±0.13	−0.01±0.09	−1.76±0.36	−0.03±0.06	0.984	12	**a−g**, **m−q**
10	(1)	−1.05±0.28	0.01±0.05	−2.40±0.20	0.01±0.07	0.999	5	**c**, **n−q**
11	(2)	−1.50±0.07	−0.06±0.04	−2.08±0.17	−0.09±0.03	0.997	11	**a−g**, **n−q**
12	(3)	−1.50±0.07		−1.90±0.10	−0.07±0.03	0.996	11	**a−g**, **n−q**

[a] s_ρ, s_δ, s_f, and s_i represent standard errors of ρ, δ, f, and i, respectively; i: intercept; R: correlation coefficient; n: number of data points. The parameter correlations were calculated by using classical σ_p substituent constants (O. Exner, *Correlation Analysis of Chemical Data*, Plenum Press, New York, London, **1988**, pp. 61−62 and 143−144).

$$\log K_{o,p}/K_H = \rho\sigma_{o,p} + fF_{o,p} + i \quad (3)$$

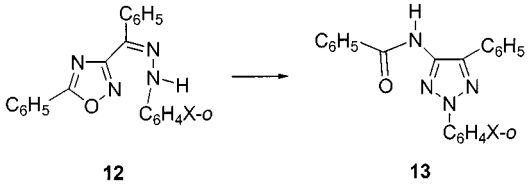
As already pointed out for *meta*- and *para*-substituted derivatives,[3d] the overall effect of X on the studied equilibrations most probably results from a balance between counteracting factors on **10** (or **10**$^-$) and/or on **11** (or **11**$^-$). Thus, when rationalising the polar effect of, for example, an electron-withdrawing substituent, one must essentially take into account: *i*) a decrease in the electron density of the nucleophilic oxygen atom of **10**, *ii*) a lower weight of resonance structures (Scheme 4) **C** and **D** of **10**, and *iii*) a disfavouring effect on the conjugation between the aryl and the heteroaryl rings of **11**, thus lowering the significance of the stabilising "diaryloid" effect.[3a]



Scheme 4

The qualitative similarity of the effects played by *ortho* and *para* substituents, attested to by the excellent correlations above, suggests that, as previously proposed for *para*-substituted derivatives,[3d] the "diaryloid" effect governs the overall outcome in neutral media, justifying the observed shift of the equilibrium towards **10** for electron-withdrawing substituents; this would essentially originate from compensation between factors *i* and *ii* and would furthermore be strongly in agreement with the observation that structures such as **C** or **D** play only a minor role in the resonance system of **10**, the main contribution being provided by the "internal" conjugation of the amido group itself (structure **B**), which is not significantly affected by electronic interactions with the aryl moiety (see below).[9] In alkaline media, on the other hand, stabilisation of **10**$^-$ by the adjacent phenyl ring is most likely to be mainly responsible for the experimental results.

At first sight, the absence of steric effects may appear surprising; as a matter of fact we have recently observed (Scheme 5) that the kinetics of the rearrangement of *ortho*-substituted (*Z*)-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**12**) into 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazoles (**13**) (like the **10/11** equilibrium, an example of the general class of monocyclic rearrangement of heterocycles[1−3]) show[14] a significant contribution of the "primary steric effect" to the overall reactivity observed[15] in dioxane/water (at $pS^+ = 3.80$: $\rho_{o,m,p} = -1.30$, $f = -0.90$, and $\delta = 0.50$; at $pS^+ = 11.50$: $\rho_{o,m,p} = 2.23$, $f = 0.31$, and $\delta = 1.51$ in the presence of electron-withdrawing substituents).



Scheme 5

To understand why the reactivities of **12** and of the **10/11** couple should be so differently affected by the steric component of proximity effects, comparison between the side chains involved in the rearrangement in the two systems appears relevant. The electronic distribution in the >C=N−N$_\alpha$H−Ar side chain of **12** is essentially characterised by the possibility of conjugative interactions between N$_\alpha$ and the aryl group, electron-withdrawing and -repelling substituents in the aryl group decreasing or increasing, respectively, the electron density on N$_\alpha$ and hence

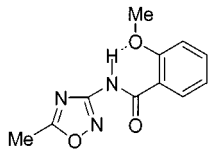
on the proton bound to N_α (i.e., the two factors that influence the reactivity in the pS^+-independent and -dependent regions). Of course, the occurrence of through-conjugation is subject to precise steric requirements that can hardly be satisfied if an *ortho* substituent is present on the aromatic ring.

In contrast, the −NH−C_αO−Ar [or −N=C(OH)Ar] side chain in **10** is essentially characterized, as already mentioned, by the strong resonance within the amido function, which is rather insensitive to the electronic effects of the aryl group. Consequently, as ^{13}C NMR spectroscopic data of *para*-substituted benzamides and 2,6-dimethylbenzamides have shown,[9] a low contribution of through-conjugation between C_α and the adjacent aryl moiety is to be expected. Their interaction is, rather, dominated by a "reverse" polar effect[16] that has been shown not to be significantly affected by 2,6-dimethyl substitution (i.e., by steric effects).

The Origin of the Peculiar Behaviour of *o*-Methoxy Derivatives 10m and 11m

For the **10m/11m** couple, the experimentally determined equilibrium constants (1.38 and 3.17 under neutral and basic conditions, respectively) differed significantly from those (K_N = 4.0, K_A = 1.2) calculated from the two-parameter Equation (3). Thus, with respect to expectations, the equilibrium was shifted more towards **10m** under neutral conditions, but towards the acetylamino anion **11m**$^-$ under basic conditions.

In neutral solution, overstabilisation of **10m** could arise from an intramolecular hydrogen-bonded structure as indicated in **14**; actually, a calculation of $\delta\Delta G°$ ($\Delta G°_{exp} - \Delta G°_{calc}$) gives a value (ca. 0.6 kcal·mol^{-1}) perfectly compatible with such a structure.[17] This hypothesis found further support in the ^{1}H NMR spectra determined in different solvents, as the N−H signal of **10m** was found at low fields both in DMSO (δ = 10.94) and in $CDCl_3$ (δ = 10.26). By contrast, the N−H signal in the *para* isomer **10a** was found at δ = 11.28 in DMSO, but at δ = 8.57 in $CDCl_3$,[18] the downfield shift in the H-bond-accepting DMSO indicating the occurrence of hydrogen-bonding with solvent molecules. In the *ortho* isomer, in contrast, only a relatively small variation in the N−H signal could be observed depending on the spectroscopic solvent used, and so we can conclude that an (intramolecular) hydrogen-bonded structure is present in both solvents (Figure 1).



14

Figure 1. Intramolecular hydrogen bond for compound **14**

Comparison with ^{1}H NMR spectra (Table 3) of other pairs of *ortho* and *para* isomers for which intramolecular hydrogen-bonded structures were not possible (**10b** and **10n**, and also **10e** and **10q**) strengthened this interpretation: the N−H signals were always observed in the δ = 7.8−8.7 range in $CDCl_3$ and in the δ = 11.4−11.8 range in DMSO for both *ortho* and *para* isomers, respectively.

Table 3. ^{1}H NMR N−H chemical shifts of compounds

Compound	δ ($CDCl_3$)	δ ([D_6]DMSO)
10a	8.57	11.28
10b	8.63	11.35
10e	8.48	11.77
10m	10.26	10.94
10n	7.81	11.41
10q	8.71	11.77

The situation observed is not new, and is reminiscent of the findings of Wooldridge et al.,[19] who reported on the occurrence of strong intramolecular hydrogen bonding between an *ortho*-alkoxy substituent and the N(1)−H proton of a series of 2-aryl-8-azopurin-6-ones. As a matter of fact, the proton of a pyrimidone ring amide group gives an intramolecular hydrogen bond with the oxygen atom of the alkoxy group. The occurrence of the intramolecular hydrogen bonding was evaluated by IR spectroscopy. The observed Δν [that is, the difference in cm^{-1} between the N(1)−H stretching frequency observed for *ortho*-alkoxy derivatives and that of the unsubstituted compound] gives a measure of the strength of the bond formed. Interestingly, the occurrence of intramolecular hydrogen bonding strongly increased the pharmacological (antiallergic) activity of the studied compounds.

Finally, as far as the situation in basic solution is concerned, a possible explanation for the observed destabilisation of **10m**$^-$ with respect to **11m**$^-$ can be found in the electrostatic repulsion between the lone pairs on the oxygen of the methoxy group and the charged heteroatoms (oxygen as well as nitrogen) of the anionic amide system.

Conclusion

Study of the **10/11** ring-degenerate equilibration of some *ortho*-substituted (X = H, OMe, Me, Cl, Br, CF_3, NO_2) derivatives has demonstrated a large contribution from purely electronic factors in determining the position of equilibrium; the contribution of the "proximity polar effect" appears much higher (> 90%) than that of the "ordinary polar effect" in neutral solution, whilst in basic solution the two effects balance almost exactly (45% and 55%, respectively). The absence of the "primary steric effect" component in this kind of ring−ring interconversion has been interpreted on the basis of the "strong" internal conjugation of the amido group, which leaves little role for the conjugation between the aryl group and N_α. Interesting proximity effects have been observed in the case of the *ortho*-methoxy derivative.

Table 4. Physical data for the acylamino-1,2,4-oxadiazoles **10m−r** and **11m−r**

Compd.	M.p. [°C][a][b]	IR [cm^{-1}]	^{1}H NMR, δ ([D$_6$]DMSO)	HRMS	Elemental analyses
10m	116−118 (A)	3250, 3200, 3100, 1665	2.60 (s, 3 H), 3.95 (s, 3 H), 7.10−7.72 (m, 4 H), 10.94 (s, 1 H)	found 233.08029 calcd. 233.08004	found C 56.72, H 4.65, N 17.98 calcd. C 56.65, H 4.74, N 18.02
10n	156−158 (A)	3240, 3210, 3080, 1690	2.39 (s, 3 H), 2.57 (s, 3 H), 7.27−8.02 (m, 4 H), 11.41 (s, 1 H)	found 217.08531 calcd. 217.08513	found C 60.58, H 5.12, N 19.20 calcd. C 60.82, H 5.10, N 19.34
10o	152−153 (A)	3240, 3190, 3100, 1665	2.62 (s, 3 H), 7.47-8.13 (m, 4 H), 11.69 (s, 1 H)		found C 50.39, H 3.26, N 17.55 calcd. C 50.54, H 3.39, N 17.68
10p	160−162 (A)	3230, 3190, 3100, 1700	2.62 (s, 3 H), 7.45−8.06 (m, 4 H), 11.70 (s, 1 H)		found C 42.39, H 2.71, N 14.81 calcd. C 42.58, H 2.86, N 14.90
10q	138 (A)[c]				
10r	145 (A)[c]				
11m	124 (B)	3240, 3150, 1690	2.17 (s, 3 H), 3.97 (s, 3 H), 7.15−8.00 (m, 4 H), 11.30 (s, 1 H)	found 233.08039 calcd. 233.08004	found C 56.81, H 4.67, N 17.88 calcd. C 56.65, H 4.74, N 18.02
11n	165 (B)	3230, 3200, 3100, 1690	2.19 (s, 3 H), 2.69 (s, 3 H), 7.46−8.06 (m, 4 H), 11.27 (s, 1 H)	found 217.08542 calcd. 217.08513	found C 60.63, H 5.16, N 19.27 calcd. C 60.82, H 5.10, N 19.34
11o	130−132 (B)	3210, 3160, 3100, 1690	2.20 (s, 3 H), 7.26−8.14 (m, 4 H), 11.38 (s, 1 H)	found 237.03091[d] calcd. 237.03050	found C 50.42, H 3.20, N 17.52 calcd. C 50.54, H 3.39, N 17.68
11p	143−145 (B)	3230, 3180, 3100, 1670	2.20 (s, 3 H), 7.45−8.06 (m, 4 H), 11.38 (s, 1 H)	found 280.98032[e] calcd. 280.97999	found C 42.64, H 2.69, N 14.76 calcd. C 42.58, H 2.86, N 14.90
11q	124 (A)[c]				
11r	163 (C)[c]				

[a] Melting points can be affected by a thermally induced rearrangement. All new compounds are colourless. [b] Crystallisation solvents: A: benzene; B: ethanol; C: ethyl acetate. [c] Ref.[21]: **10q**: m.p. 138 °C; **10r**: m.p. 145 °C; **11q**: m.p. 124 °C; **11r**: m.p. 163 °C. [d] ^{35}Cl isotope. [e] ^{79}Br isotope.

Experimental Section

General Remarks: Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra (Nujol) were determined with a Perkin−Elmer 257 instrument, ^{1}H NMR spectra were recorded with a Bruker 250 E spectrometer (tetramethylsilane as internal standard). Analytical determinations were carried out by ^{1}H NMR, integrating the methyl singlets in the ranges δ = 2.39−2.62 (characteristic of 5-methyl of **10**) and 2.17−2.20 (characteristic of the 3-acetylamino group of **11**), respectively. Compositions at equilibrium (expressed in % of the two isomers) represent average values (with an uncertainty lower than ±2%) of at least three independent determinations. Compounds **10** were prepared by treatment of 3-amino-5-methyl-1,2,4-oxadiazole[20,21] with the appropriate aroyl chloride by the procedure previously described.[3a,3d,7] Compounds **11** were prepared by isoheterocyclic rearrangement of the corresponding **10** by refluxing for several hours in ethanol. After removal of the solvent, the mixtures of **10** and **11** were separated by chromatography. Compounds **11q** and **11r** were prepared by acetylation of 3-amino-5-aryl-1,2,4-oxadiazoles with acetyl chloride in pyridine.[21] All new compounds gave satisfactory analytical data (C, H, N). Significant physical data are collected in Table 4.

Equilibration between 3-Aroylamino-5-methyl-1,2,4-oxadiazoles 10 and 3-Acetylamino-5-aryl-1,2,4-oxadiazoles 11

In CD$_3$OD: Samples of 3-aroylamino-5-methyl-1,2,4-oxadiazoles **10** ($1.8\cdot10^{-2}$ mmol) in CD$_3$OD (1 mL) were maintained in NMR tubes at 313.15 K until constant mixture composition. Equilibrium was reached in 3−5 weeks, except for the **10m/11m** couple, which required 8 weeks. Representatively, the equilibration reaction was also carried out starting from 3-acetylamino-5-aryl-1,2,4-oxadiazoles (i.e., **11m−n**), with the same equilibrium compositions being observed.

In CD$_3$OD in the Presence of *t*BuOK: Samples of 3-aroylamino-5-methyl-1,2,4-oxadiazoles **10** ($1.8\cdot10^{-2}$ mmol) in CD$_3$OD (1 mL) containing *t*BuOK ($3.6\cdot10^{-2}$ mmol)[22] reached equilibrium after standing for 30 min and were then analysed by NMR. Representatively, the equilibration reaction was also carried out starting from 3-acetylamino-5-aryl-1,2,4-oxadiazoles (i.e., **11m−n**), the same equilibrium compositions being observed.

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