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Large Chiral Recognition in Hydrogen-Bonded Complexes and Proton Transfer in Pyrrolo[2,3-*b*]pyrrole Dimers as Model Compounds

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The chiral recognition in the formation of hydrogen-bonded (HB) dimers of 1,6a-dihydropyrrolo-[2,3-*b*]pyrrole derivatives as well as in their proton-transfer processes have been studied by means of ab initio calculations. The heterochiral dimers are in general the most stable ones, but amphiprotic substituents that are able to form attactive interactions with twin groups revert this tendency. Energy differences up to 4.0 kcal/mol have been found favoring the homo- or heterochiral complexes. Two possible proton-transfer processes have been studied, the concerted one and the nonconcerted one. The compresion of the systems in the transition structures produce an increase in the energetic differences when compared to the corresponding minima complexes. A Steiner–Limbach relationship has been found for the geometrical properties of the HB in the minima and transition states calculated here. The electron density and its Laplacian at the bond critical point have been found to correlate with the HB distance.

Introduction

The main components of the biopolymers, proteins and nucleic acids, have been selectively chosen during the evolution in a unique chiral form, L-amino acids and D-sugars. Several mechanisms that could be responsible of this selection have been recently reviewed by Cintas et al.[1,2]

The different reactivities of pure enantiomeric and racemic mixtures, as proposed by Wynberg and Feringa in 1976,[3] is based on the difference in what they called the “enantiomeric recognition” effect in the former case and “antipodal interaction” in the latter. In the same year, Craig and Mellor[4] reviewed the energetic sources of the chiral discrimination in intermolecular interactions.

Experimentally, enantiodifferentiation through hydrogen-bonded complexes is present in liquid chromatographic separation of enantiomers,[5] in supramolecular chemistry (self-assemblies),[6,7] in the application of chiral additives such as Pirkle’s alcohol in NMR,[8] in the crystallization of racemic mixtures,[9] and in the recognition of biomolecules.[10]

Studies of chiral clusters in the gas phase have been carried out in recent years using different spectroscopic techniques. King and Howard reported a microwave study of the heterochiral dimer of 2-butanol.[11] Suhm et al. have studied the dimers of glycidol by means of FTIR spectroscopy.[12] Beu and Buck found evidence of the presence of different chiral isomers in the IR spectra of hydrazine clusters.[13] Zehnacker–Rentien et al. have studied the complexes of 2-naphthyl-1-ethanol with chiral systems using IR/UV double-resonance spectroscopy.[14] Speranza et al. used resonance-enhanced two-photon ionization (R2PI) spectroscopy to study the chiral complexes of alcohol dimers[15] and mass spectrometry in metallic complexes of α-aminophosphonic acids.[16]

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Only a few theoretical articles have been devoted to the study of the chiral discrimination in hydrogen-bonded complexes using ab initio methods. Leutwyler and coworkers[17] studied the interaction of the two isomers of HOOH and chiral derivatives of oxirane using MP2 and B3LYP computational methods. The largest energetic difference found was 0.46 kcal/mol. Dyczmons studied six structures of the hydrazine dimer, showing that one of the heterochiral dimers was about 0.5 kcal/mol more stable than the most stable of the homochiral structures.[18] In addition, some of us studied the self-discrimination of a series of β-amino alcohols.[19] In all the cases considered, the most stable dimer was the heterochiral one (*RS* or *SR*) up to 1.60 kcal/mol. However, when the solvent effect was considered, the stability of several of the complexes was reversed in favor of the homochiral one (*RR* or *SS*). The same authors analyzed the complexation of compounds with axial chirality.[20] The results show that in some cases oxygen−oxygen secondary interactions are able to favor the homochiral complex versus the heterochiral complex.

In this paper, the homo- and heterochiral self-association of 1*H*-1,6a-dihydropyrrolo[2,3-*b*]pyrrole derivatives have been studied using density functional theory (DFT) (B3LYP/6-31+G**) and ab initio (MP2/6-311+G**) methods. In addition, two possible proton-transfer mechanisms in the dimers, concerted and nonconcerted, have been studied in the calculated complex and its influence to the chiral recognition has been explored. The electron density of the dimers has been characterized with the atoms in molecules (AIM) methodology.

Methods

The geometry of the monomers and complexes has been optimized with the B3LYP[21] hybrid HF-DFT functional and the 6-31+G** basis set[22] within the Gaussian-98 program package.[23] Frequency calculations at the B3LYP/6-31+G** level have been carried out to characterize the minimum, transition state (TS), or second-order saddle points. Further geometry optimization has been carried out at the MP2/6-311+G** level.[24] The results obtained at the B3LYP/6-31+G** and MP2/6-311+G** levels for the present study are similar without presenting qualitative discrepancies in the properties analyzed here. The interaction energy has been corrected with the inherent basis set superposition error (BSSE)[25] and zero-point energy (ZPE). The latter has been calculated only for the structures optimized at the B3LYP/6-31+G** level and used without scaling. The electron density of the complexes has been explored using the atoms in molecules (AIM) methodology[26] and the AIMPAC package.[27]

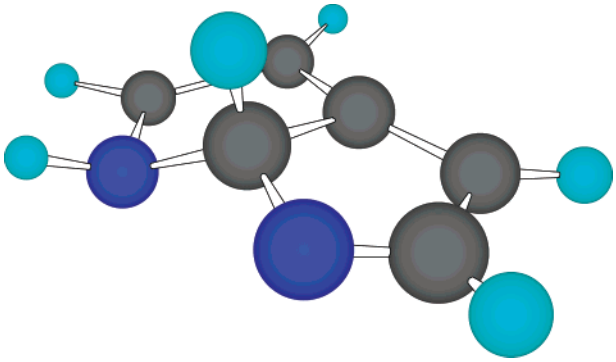

FIGURE 1. Optimized geometry of the unique conformation of the parent compound (X = H).

Results and Discussion

To study the enantiodifferentiation, we selected the 1,6a-dihydropyrrolo[2,3-*b*]pyrrole scaffold based on our previous experience with azapentalenes.[28] These compounds have a tendency to exist in an aromatic tautomeric form when X = H. Otherwise, their synthesis could be achieved by standard procedures. Besides, imidazoles and/or pyrazoles could replace pyrrole rings; the additional N atoms should provide stability without modifying the basic problem of chiral recognition.

The skeleton of the pyrrolopyrrole derivatives presents a roof shape with a unique disposition of the NH group in cis to the substituent in position 6a. The conformational uniqueness simplifies the study of the potential complexes (Figure 1).

Two homo- and two heterodimers have been studied for the parent compound (X = H). A pair of complexes (A in Figure 2) show two symmetrical NH···N hydrogen bonds, and another pair (B in Figure 2) show one NH···N and one CH···N interactions. Even though both configurations are minima, the second one is about 6.4 kcal/mol less stable than the first one. The most stable dimers (A) show C_2 and C_i symmetries for the homo- and heterochiral complexes, respectively. These configurations have been considered for the rest of the cases studied here.

In the homochiral complexes, the substituents in position 6a of the two interacting molecules are above the average plane of the molecular skeleton, while in the heterochiral complexes they are at opposite positions with respect to the average molecular plane. This geometrical disposition favor the heterochiral complex, the difference in the parent compound being 0.4 kcal/mol. Table 1 shows the results for other complexes, and in general, as the

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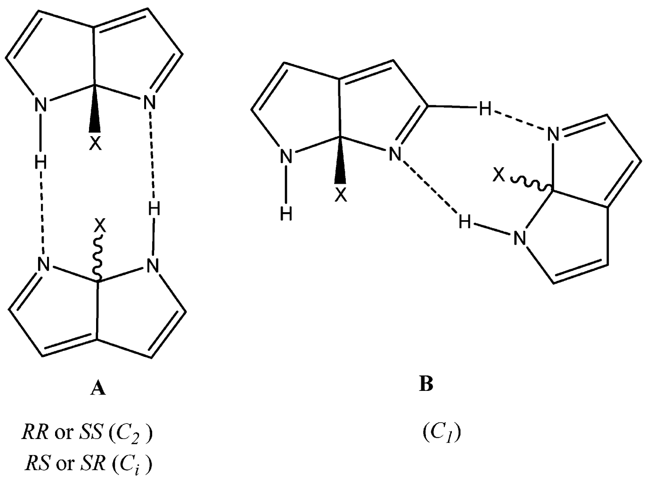

FIGURE 2. Schematic representation of the complexes studied with their corresponding symmetry.

TABLE 1. Relative and Corrected Interaction Energy at the B3LYP/6-31+G Level (the MP2/6-311+G** Results Are Shown in Parentheses) of Calculated Dimers (Configuration A in Figure 2)**

X	chirality	E_{rel}	$E_{\mathrm{I(corr)}}$
H	*R*/*R*	0.00 (0.00)	−12.57 (−13.29)
H	*R*/*S*	−0.42 (−0.36)	−13.03 (−13.55)
F	*R*/*R*	0.00 (0.00)	−8.93 (−9.50)
F	*R*/*S*	−0.61 (0.61)	−9.51 (−10.02)
Cl	*R*/*R*	0.00 (0.00)	−9.47 (−11.17)
Cl	*R*/*S*	−1.27 (−1.27)	−10.70 (−12.05)
CH_3	*R*/*R*	0.00 (0.00)	−11.09 (−13.19)
CH_3	*R*/*S*	−1.58 (−1.98)	−12.44 (−14.91)
CN	*R*/*R*	0.00 (0.00)	−9.22 (−11.42)
CN	*R*/*S*	−2.29 (−1.84)	−11.56 (−13.10)
CCH	*R*/*R*	0.00	−8.96
CCH	*R*/*S*	−0.97	−9.96
CF_3	*R*/*R*	0.00	−7.97
CF_3	*R*/*S*	−2.11	−9.98
CCl_3	*R*/*R*	0.00	−3.66
CCl_3	*R*/*S*	−3.27	−6.57
$C(CH_3)_3$	*R*/*R*	0.00	−7.20
$C(CH_3)_3$	*R*/*S*	−1.88	−9.17
$Si(CH_3)_3$	*R*/*R*	0.00	−8.98
$Si(CH_3)_3$	*R*/*S*	−2.82	−11.78
SiF_3	*R*/*R*	0.00	−9.77
SiF_3	*R*/*S*	−2.65	−12.25
$SiCl_3$	*R*/*R*	0.00	−6.99
$SiCl_3$	*R*/*S*	−4.04	−10.48

size and electrostatic repulsion of the X group increase, the chiral discrimination is larger reaching values up to −4.0 kcal/mol.

The substituents studied so far are unable to form attractive interaction with an identical group in another molecule, and thus, the heterochiral complexes are more stable than the homochiral ones. The study of derivatives with amphiprotic groups that can act as hydrogen-bond donors and acceptors in position 6a can reverse this tendency (Table 2). The two cases with amphiprotic substituents studied here show a chiral discrimination in favor of the homochiral complex up to 2.7 kcal/mol.

The largest interaction energies of the complexes correspond to that of the parent compounds and the methyl derivative with corrected interaction energies up to −14.9 kcal/mol. Bulky and electronically repulsive substituents reduce the interaction energies up to −3.7 kcal/mol for the homochiral dimer of the trichloromethyl derivative.

TABLE 2. Relative and Corrected Interaction Energy at the B3LYP/6-31+G Level (the MP2/6-311+G** Results Are Shown in Parentheses) of Calculated Dimers with Diprotic Substituents (Configuration A in Scheme 1)**

X	chirality	E_{rel}	$E_{\mathrm{I(corr)}}$
OH	*R*/*R*	0.00 (0.00)	−6.26 (10.70)
OH	*R*/*S*	2.28 (1.24)	−4.94 (−10.08)
NH_2	*R*/*R*	0.00 (0.00)	−9.23 (−14.78)
NH_2	*R*/*S*	2.65 (2.74)	−7.32 (−12.82)

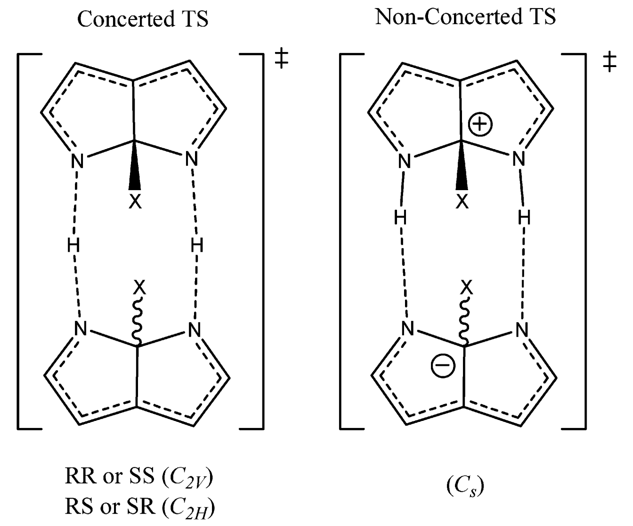

FIGURE 3. Schematic representation of the transition states studied with their corresponding symmetry.

The geometries of the HB of the dimers show nonlinear disposition with a NH···N angle between 150 and 160° and an HB distance approximately of 2.0 Å. In all the cases of the first set of compounds, the heterochiral dimer shows shorter N···H distance than the corresponding homochiral one, the largest difference 0.12 Å for the trichlorosilyl complex as an indication of the strongest HB interaction.

Two different possible proton-transfer mechanisms have been studied, the concerted and the nonconcerted ones (Figure 3). In the case of the concerted transition state (TS), the complexes adopt C_{2v} and C_{2h} symmetries for the homo- and heterochiral complexes, respectively. In all cases, these structures show two imaginary frequencies. The nonconcerted TS structures present a C_s symmetry and a unique imaginary frequency as an indication of true TS.

The energetic values of the TS show in all cases slightly larger values for the MP2 calculations than in the B3LYP ones. These results are in concordance with previous reports that have shown that DFT calculations underestimated TS barriers.[29]

In all cases, small energetic differences are found between the nonconcerted and concerted TS structures for each case, the largest difference being 1.2 kcal/mol.

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TABLE 3. Energetics of the Transition States (kcal/mol)

		nonconcerted TS			concerted TS		
X	chirality	E_{rel}	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	E_{rel}	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$
H	*R*/*R*	0.00	14.41	10.89	0.00	15.41	8.97
		(0.00)	(17.61)	(14.09)	(0.00)	(18.42)	(11.98)
H	*R*/*S*	−1.01	13.93	10.43	−0.90	14.82	8.52
		(−1.09)	(17.01)	(13.51)	(−0.96)	(17.69)	(11.39)
F	*R*/*R*	0.00	18.63	14.30	0.00	19.29	12.65
		(0.00)	(26.11)	(21.78)	(0.00)	(26.56)	(19.91)
F	*R*/*S*	−1.43	17.89	13.58	−1.35	18.47	11.93
		(−1.28)	(25.45)	(21.14)	(−1.26)	(25.89)	(19.35)
Cl	*R*/*R*	0.00	17.64	13.51	0.00	18.44	11.76
		(0.00)	(22.34)	(18.20)	(0.00)	(22.76)	(16.09)
Cl	*R*/*S*	−2.09	16.87	12.89	−2.04	17.61	11.10
		(−1.64)	(21.83)	(17.85)	(−1.78)	(22.39)	(15.88)
CH_3	*R*/*R*	0.00	14.51	11.37	0.00	15.60	9.46
		(0.00)	(17.35)	(14.21)	(0.00)	(18.29)	(12.15)
CH_3	*R*/*S*	−1.96	14.02	10.93	−2.07	15.22	8.97
		(−2.97)	(16.38)	(13.29)	(−2.95)	(17.29)	(11.04)
CN	*R*/*R*	0.00	15.38	11.66	0.00	16.16	9.85
		(0.00)	(20.28)	(16.56)	(0.00)	(20.85)	(14.54)
CN	*R*/*S*	−3.20	14.42	10.91	−3.25	15.25	9.05
		(−3.13)	(18.79)	(15.29)	(−3.32)	(19.56)	(13.37)

The inclusion of the ZPE correction (smaller in the concerted TSs than in the nonconcerted ones) inverts the energetic stability of these TSs.

The proton-transfer transition states produce a compression of the complexes in order to favor the energetic barrier or the process.[30] In the present case, the compression of the N···N distance is about 0.4 and 0.35 Å for the concerted and nonconcerted TS structures, respectively. All the concerted structures studied here present very similar interatomic N···H distances (between 1.284 and 1.286 Å) and N···N atoms (between 2.542 and 2.552 Å) as an indication of the important structural limitation of these TS.

The chiral discrimination in the TS structures is larger than those of the corresponding minima up to 1.5 kcal/mol (Table 3). The compression of the systems, which produce shorter distances between the X groups for the homochiral transition state, should be the reason for the increase in the energetic differences between the homo- and heterochiral complexes. However, on the basis of these observations, the concerted TS structures should provide larger differences than the corresponding nonconcerted TS ones, and this is only true for the methyl and cyano derivatives.

Using the geometries of all the minima and transition states calculated at the B3LYP/6-31+G** level, a Steiner−Limbach correlation[31,32] of the HB distances can be obtained. This correlation is based on the Pauling concept of the total valence of the hydrogen atom involved in the HB should be equal to 1 (eq 1).[33] The parameter r_0 represents the bond distance for the isolated system, and b is an adjustable parameter that in general has a value of approximately 0.4. Equation 1 can be rewriten as eq 2, which depends on the sum and difference of the NH distances (r_1 and r_2, Scheme 1). Since in this case the two heavy atoms involved are the same, r_1 and r_2 are interchangeable. Figure 4 shows the mentioned correlation and how the points are grouped in the minima structures (larger values of "$r_1 + r_2$"), nonconcerted transitions state ones (intermediate values of $r_1 + r_2$) and concerted transition state geometries (zero values of $r_1 - r_2$). It should be noted that all the cases considered here are nonlinear with NHN angles that vary from 150 to 165°.

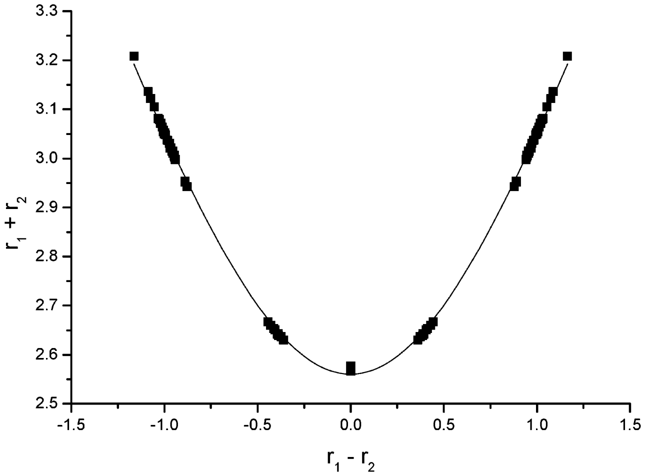
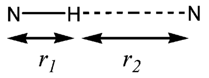


FIGURE 4. Steiner−Limbach correlation of the geometrical parameters for minima and TS structures calculated here. The fitted curve corresponds to eq 2 and to the following adjusted parameters: $r_0 = 0.9885 \pm 9 \times 10^{-4}$, $b = 0.421 \pm 0.002$, $r^2 = 0.999$, $n = 96$.

SCHEME 1



$$e^{(r_0 - r_1)/b} + e^{(r_0 - r_2)/b} = 1 \qquad (1)$$

$$(r_1 + r_2) = 2r_0 + (r_1 - r_2) + 2b\ln(1 + e^{-(r_1 - r_2)/b}) \qquad (2)$$

The analysis of the electron density of the complexes within the AIM methodology show bond critical points in the formed HB as well as in the transition-state structures for all the N···H moieties. As shown previously, a join function is needed to correlate the data in the whole range of distances.[34] In the present case, the distributions of the points do not cover the range of the distances in a uniform way and the fitting of the join function presents serious difficulties. To overcome this problem, a reaction coordinate between the minimum and the nonconcerted transition state for the RS complex, X = H, have been calculated. For each point of the reaction coordinate, four different N···H moieties are obtained since the structures lack any symmetry.

The data corresponding to the stationary structures and those of the reaction coordinate nicely overlap in all the regions considered (Figure 5). Using all the data, excellent fits have been found for the electron density

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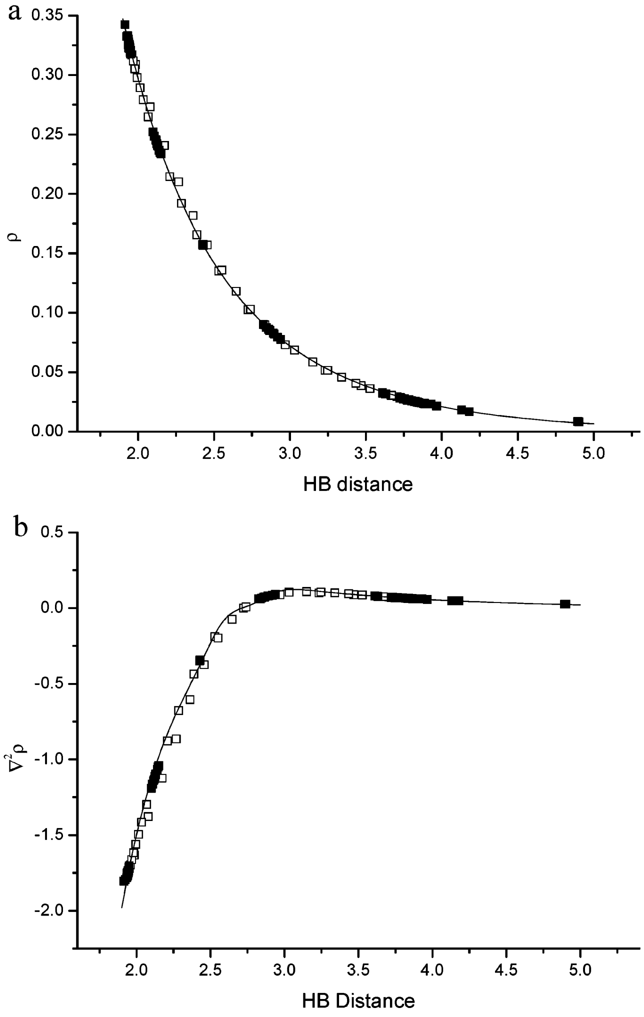

FIGURE 5. Electron density (a) and Laplacian (b) at the bond critical point vs the HB distance (au). The fitted curves corresponds to the join functions as described in ref 34.

and the Laplacian vs the HB distance (see Figure 5), which indicated the generality of these correlations.

Additional bond critical points have been found for all the *RR* complexes between the groups located in the 6a position. Even though the presence of a bond critical point has been interpreted as an indication of attractive forces between the two atoms involved,[35] it could disrupt other stronger interactions as, in the present case, the hydrogen bonds formed between the two monomers.

Conclusion

A theoretical study of the characteristics of the homo- and heterochiral dimers of a series of derivatives of 1,6a-dihydropyrrolo[2,3-*b*]pyrrole at B3LYP/6-31+G** and MP2/6-311+G** computational levels have been carried out. The hetero- or homochiral energetic preferences have been modulated using monoprotic or amphiprotic substituents, respectively. The energetic differences obtained are up to 4.0 kcal/mol.

In addition, the concerted and nonconcerted proton transfer mechanisms have been studied. In both cases, the energetic differences found are larger than in the corresponding minima due to the compression of the dimers. Probably the enzymes use a similar mechanism to discriminate between different substrates or even enantiomers.

The geometries of all the cases studied nicely fit in a Steiner−Limbach plot that correlates the relative position of the proton with the sum of the distances of the proton to the heavy atoms.

The study of the electron density has allowed to fit the electron density and its Laplacian versus the N···H interatomic distance ranging from covalent bonds to weak HBs.

Finally, although the studied compounds have never been synthesized they open a new entry to the study of chiral recognition in simple organic molecules.

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Supporting Information Available: Tables with the total energy of the complexes and transition states calculated at the B3LYP/6-31+G** and MP2/6-311+G** levels and Cartesian coordinates of the minima. This material is available free of charge via the Internet at http://pubs.acs.org.

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