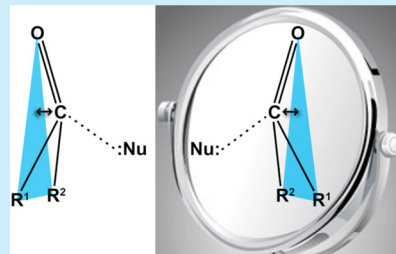


$n \rightarrow \pi^*$ Interactions Engender Chirality in Carbonyl Groups

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ABSTRACT: An $n \rightarrow \pi^*$ interaction stems from the delocalization of the electron pair (n) of a donor group into the antibonding orbital (π^*) of a carbonyl group. Crystallographic analyses of five pairs of diastereoisomers demonstrate that an $n \rightarrow \pi^*$ interaction can induce chirality in an otherwise planar, prochiral carbonyl group. Thus, a subtle delocalization of electrons can have stereochemical consequences.



“Noncovalent” interactions can involve electron delocalization and thus partial covalency. For example, the partial covalency in a hydrogen bond stems from delocalization of the electron lone pair (n) of the hydrogen-bond acceptor into the antibonding orbital (σ^*) of the hydrogen bond donor.¹ Similarly, the partial covalency in an $n \rightarrow \pi^*$ interaction stems from the delocalization of the electron pair (n) of a donor group into the antibonding orbital (π^*) of a carbonyl group.² This interaction is reminiscent of the Bürgi–Dunitz trajectory for nucleophilic addition to carbonyl groups.³ In common protein secondary structures, the electron-pair donor is a proximal amide oxygen in the backbone.^{2*gi*} The partial covalency in these interactions induces an intimate association of the interacting donor and acceptor groups, wherein their van der Waals surfaces interpenetrate.

Recently, we proposed that an $n \rightarrow \pi^*$ interaction can engender experimentally detectable pyramidalization of a planar carbonyl group.^{2*a*} In this pyramidalization, the acceptor carbonyl carbon would be displaced toward the donor and away from the plane formed by the three atoms linked to the carbonyl carbon (Figure 1). Such pyramidalization would

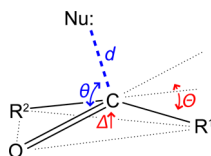


Figure 1. Parameters describing carbonyl group pyramidalization due to an $n \rightarrow \pi^*$ interaction.

transform an otherwise prochiral carbonyl group into a chiral entity.^{4,5} Although analogous distortions have been noted for reactive carbonyl groups (e.g., ketones) proximal to potent nucleophiles (e.g., amines),³ it is less clear if they can result from an $n \rightarrow \pi^*$ interaction involving weak nucleophiles, such as the oxygen of a carbonyl group. If pyramidalization were to result from such a weak force, its magnitude would be small,^{2*y,6*}

requiring that crystal structures be solved by direct methods rather than by experimental phasing or molecular replacement. Even so, any observed pyramidalization could be attributable to the packing of the crystal lattice or other forces.⁷

To overcome such artifacts, we sought to determine the crystal structures of diastereoisomers that differ in the position of one of two putative electron-pair donors with respect to an acceptor carbonyl group in the same molecule. We reasoned that if the displacement of the carbonyl carbon correlated with the position of the donor, then an $n \rightarrow \pi^*$ interaction is responsible for the carbonyl pyramidalization. Conversely, the lack of such a correlation would implicate other forces.

Previously, we showed that installation of a fluoro group at C^{γ} of AcProOMe enlists a gauche effect.⁸ In the R configuration, a fluoro group enforces a C^{γ} -exo ring pucker, which brings the donor and acceptor carbonyl groups together for a strong “frontal” $n \rightarrow \pi^*$ interaction.⁹ Conversely, in the S configuration, a fluoro group enforces a C^{γ} -endo ring pucker, which allows for only a weak $n \rightarrow \pi^*$ interaction between the more distal donor and acceptor carbonyl groups.⁹ The endo pucker does, however, place the S -configured fluoro group in close proximity to the other “rear” face of the carbonyl group. We envisioned that a transannular $n \rightarrow \pi^*$ interaction¹⁰ can be effected by this “rear” face of the carbonyl if the S -configured fluoro group is replaced with a good electron-pair donor.¹¹ The direction of carbonyl carbon displacement induced by a “rear” $n \rightarrow \pi^*$ interaction would be opposite to that effected by the “frontal” $n \rightarrow \pi^*$ interaction.

To test this hypothesis, we synthesized and examined by X-ray crystallography structures of five pairs of diastereoisomers (1–5) with “frontal” or “rear” $n \rightarrow \pi^*$ interactions arising from the R and S diastereoisomers, respectively (Figure 2). We quantified the extent of pyramidalization by using the parameters Δ and Θ (Figure 1). In accordance with our

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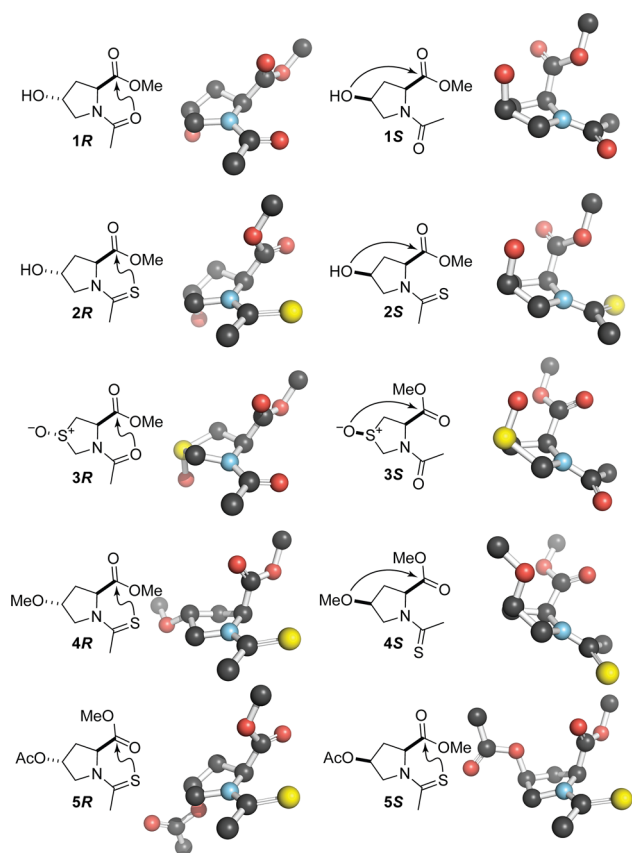


Figure 2. $n \rightarrow \pi^*$ Interactions that elicit carbonyl group pyramidalization in five pairs of diastereoisomers (1–5). Structures show non-hydrogen atoms as determined by X-ray crystallography. For computational analyses of $n \rightarrow \pi^*$ interactions in crystalline 1–5, see Figure S7 and Table S37 in the Supporting Information.

hypothesis, we found that the displacement of the carbonyl carbon is always toward the electron-pair donor that is proximal to the acceptor carbonyl carbon (Figure 2 and Table 1).

Table 1. Structural Parameters for Crystalline Compounds 1–5

compd	donor atom	$C'_i=O_i$ face	d (Å)	θ (deg)	Δ (Å)	Θ (deg)
1R ^a	O	re	2.83	91.8	0.017	2.1
1S ^b	O	re	2.95	100.1	0.027	3.3
2R	S	re	3.05	105.7	0.041	5.0
2S	O	re	2.86	106.0	0.013	1.6
3R ^c	O	re	3.01	91.9	0.025	2.9
3S ^c	O	si	2.93	98.9	0.054	6.3
4R	S	re	3.31	103.1	0.026	3.0
4S	O	si	3.02	100.3	0.025	3.0
5R	S	si	3.03	106.5	0.053	6.3
5S	S	re	3.37	92.3	0.007	0.8

^aData from ref 12. ^bData from ref 21. ^cData from ref 2m.

Compounds 1 and 5 offer particular insight. In crystalline 1R and 1S, the *re* face of the carbonyl group is exposed to an $n \rightarrow \pi^*$ interaction from two distinct donors (Figure 2). In crystalline 5R and 5S, the *si* or *re* face, respectively, of the carbonyl group is exposed to an $n \rightarrow \pi^*$ interaction from the same donor. Despite these distinctions, the displacement of the carbonyl carbon in all four of these compounds is always toward the donor (Table 1).

These analyses indicate that carbonyl pyramidalization does indeed result from $n \rightarrow \pi^*$ electronic delocalization. The induction of a stereogenic center is thus a signature of the $n \rightarrow \pi^*$ interaction. Integrating the solid-state data herein with solution-state data from infrared spectroscopy^{2j,l,9a,13} indicates that, despite being relatively weak, an $n \rightarrow \pi^*$ interaction can have important consequences for carbonyl groups.

The ten crystal structures have other notable features. Six of the diastereoisomers adopt a ψ dihedral angle ($N_i-C'_i-C'_{i+1}-N_{i+1}$ but with an oxygen replacing N_{i+1}) close to that in a right-handed α -helix ($\psi \approx -45^\circ$; 1R, 3R, 3S, 4R, 4S, and 5S), whereas four adopt a ψ dihedral angle close to that in a left-handed polyproline II helix ($\psi \approx 150^\circ$; 1S, 2R, 2S, and 5R). Evidently, either of these rotamers can gain stability from a “frontal” or “rear” $n \rightarrow \pi^*$ interaction. In addition, all five of the *R* diastereoisomers have a *trans* (*Z*) amide bond, whereas three of the *S* diastereoisomers have a *cis* (*E*) amide bond (1S, 3S, and 4S). These data are consistent with the *trans* amide bond being stabilized by a “frontal” $n \rightarrow \pi^*$ interaction,¹⁴ which is weaker in the presence of a “rear” $n \rightarrow \pi^*$ interaction.^{2v,11} The bridging acetoxy oxygen of 5S is the weakest transannular donor in 1S–5S and alone fails to manifest a significant “rear” $n \rightarrow \pi^*$ interaction.

Our data provide insight, in particular, on oxygen versus sulfur as a donor for an $n \rightarrow \pi^*$ interaction. The pyramidalization effected by the thioamide donor in 2R is much greater than that by the isosteric amide donor in 1R (Table 1). This observation is consistent with a quantum mechanical basis for the $n \rightarrow \pi^*$ interaction, as we have described elsewhere.^{2a,u} An oxygen can, however, be a strong donor, as in 3S. Although a sulfoxide is not a true isostere of a carbonyl group, its use to enhance an $n \rightarrow \pi^*$ interaction merits consideration.

Our findings have general implications. Carbonyl pyramidalization has been reported in protein structures determined at high resolution.^{2y,6} These deformations could stem from an $n \rightarrow \pi^*$ interaction. As the nitrogen of peptide bonds can be pyramidal,¹⁵ our data suggest that every backbone atom in a protein (except C^α of glycine residues) can be a stereogenic center. Moreover, pyramidalization of a carbonyl carbon could be accompanied by increased electron density on the carbonyl oxygen,¹⁶ making that oxygen a better hydrogen-bond acceptor. Such enhanced chirality and hydrogen-bonding ability might play unappreciated roles in biomolecular recognition processes. Finally, we note that $n \rightarrow \pi^*$ interactions have the potential to relay chirality through a polypeptide or other organic polymer.

■ ASSOCIATED CONTENT

Supporting Information

Procedures for the synthesis and crystallographic analysis of compounds 2, 4, and 5, and results from computational analyses of $n \rightarrow \pi^*$ interactions in crystalline 1–5. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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