

A theoretical investigation of the CO₂-philicity of amides and carbamides

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Abstract The knowledge of the interactions taking place at a molecular level can help the development of new technological procedures in Chemistry with low environmental impact. In organic, biochemical and pharmaceutical synthesis and in analytical chemistry, important advances in this domain are related to the use of solvents that can be valid alternatives to hazardous organic solvents. In the last decades, a large emphasis has been given to the use of carbon dioxide under supercritical conditions, since the mild temperature and pressure conditions of the fluid can easily be controlled to improve its capacity to solubilize small organic compounds. On the other hand, the solubility

of larger molecules and of polar compounds in this medium is generally very low. This has motivated recent theoretical and experimental studies with the purpose of reaching a better understanding of the so-called CO₂-philicity of molecules and materials, and very encouraging results have been reported. In this paper, we present an ab initio study of the intermolecular interactions between CO₂ and amide and carbamide derivatives, performed on model 1:1 complexes at the MP2/aug-cc-pVTZ//MP2/aug-cc-pVDZ level. Our findings shed some light on the key points to be considered in the design of large CO₂-philic molecules, hinting at the use of solubilizer groups in which amide or urea bonds could be involved.

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1 Introduction

Supercritical carbon dioxide (scCO₂) is becoming an important commercial and industrial solvent and has attracted increasing attention for the development of green chemical processes. In addition to its low toxicity and environmental impact, scCO₂ is readily available since its critical point is characterized by a critical temperature of 31.1 °C and a critical pressure of 7.4 MPa [1–4].

However, a strong limitation to a wider use of industrial technologies based on this solvent is related to the low solubility of large molecules and of polar compounds. A clear picture of the intermolecular interactions that can be exploited to trigger a better solubility is therefore necessary to assist in the design of organic, biochemical and pharmaceutical synthesis/separation procedures taking place in

scCO₂. In the past years, different studies have tried to propose new routes to an improved CO₂-philicity, a concept that was introduced by analogy with the properties of aqueous systems and which has been related to Lewis acid/base (LA–LB) interactions. The first success in the design of CO₂-philic materials was achieved with the development of fluorinated polymers [5]. However, the technology used for fluorination is quite expensive, and it can be problematic from the environmental viewpoint [6]. The interpretation of the CO₂-philic character of fluorinated compounds, based on experimental and theoretical investigations, has been reviewed in Ref. [6]. Some specific interactions between the F atom and the electron-poor C atom of CO₂ have been pointed out, in addition to an influence of F on the acidity of neighboring H atoms, which makes them H-bond donors with respect to the O atoms of CO₂.

The search for non-fluorous molecules soluble in scCO₂ was stimulated by some work pointing out LA–LB interactions between CO₂ and polymers possessing electron-donating functional groups such as the carbonyl group [7]. In the following years, a great deal of work has been devoted to the CO₂-philicity of carbonyl derivatives, including the synthesis of functionalized silicones [8], of diglycolic acid esters [9], and of amide derivatives [10, 11]. A high CO₂-solubility has been found for sugar derivatives and for poly(ether-carbonate) copolymers [12, 13]. Oligomeric surfactants based on glycol ethers have been developed with a different purpose, such as CO₂ capture, to improve the absorption of excess CO₂ from the atmosphere [14]. It is worth mentioning that some non-fluorous, non-carbonyl compounds have also been shown to be soluble in CO₂, among which bipyridine derivatives [15], polycyclic aromatic hydrocarbons [16], and some recently synthesized hybrid surfactants [17].

To complement the experimental knowledge of these interactions, quantum chemistry studies have been carried out, in particular for complexes formed by CO₂ with carbonyl derivatives [5, 18–28]. The references here reported were discussed in depth elsewhere [26]. Complexes of CO₂ with ethylene and acetylene have also been described [29]. In general, it has been shown that these complexes are stabilized by LA–LB interactions and that the CO₂ molecule behaves as a Lewis acid, in accord with the usual chemical concepts. However, in a recent study [30], we discovered that unconventional four-membered ring structures exist for CO₂-carbonyl compound complexes, in which CO₂ behaves cooperatively as both a Lewis base and a Lewis acid and which are at least as stable as the traditional structures. In subsequent work [26], we have reported a systematic investigation at the MP2 and CCSD(T) levels of complexes between CO₂ and aldehydes, ketones and esters together with some fluorinated

derivatives. We have shown that the LB character of CO₂ is inoperative in the interaction with aldehydes, while it plays a key role in the interactions with ketones and esters, especially in the case of fluorinated derivatives. Experimental data on some of these 1:1 complexes were available, thus allowing us to validate our theoretical procedure.

Some recent and encouraging experimental work has reported high scCO₂ solubilities for newly synthesized amide derivatives [10, 11]. Moreover, the organic synthesis of carbamide derivatives has been successfully carried out in scCO₂ through a reaction scheme in which CO₂ is at the same time a reactant and the reaction medium, instead of the usual method in organic solvents that employs hazardous reagents such as phosgene [31]. Motivated by these new findings, in this work we provide a theoretical investigation about the nature of solute–solvent interactions for amides and carbamides. Indeed, these compounds display a conjugated π system involving the p_z orbitals of the O, C and N atoms, and the interactions with CO₂ might present significant differences with respect to carbonyl derivatives studied in Ref. [26] that need to be addressed. The basic molecules formamide and urea together with some derivatives obtained from the latter by methylation were included in our study.

The electronic features that can explain the CO₂-philicity of the amide and urea bonds were investigated by means of ab initio calculations for a set of 1:1 complexes, comprising geometry optimization, calculation of the interaction energies, natural bond analysis and a study of the molecular orbitals involved in the intermolecular interactions.

2 Computational methodology

The relative energetic stability and the electronic properties of the complexes formed by CO₂ with the following molecules were studied: formamide, acetamide, *N*-methylacetamide, *N,N*-dimethylacetamide, azetidin-2-one, *N*-methylazetidin-2-one, urea, *N*-methylurea and *N,N'*-dimethylurea. When different cis/trans isomers were possible, all the corresponding complexes were taken into account (see Section III for further details). The whole list of investigated molecules and cis/trans isomers is summarized in Fig. 1.

Geometry optimization for all the monomers and the complexes were carried out at the second-order perturbation theory level (MP2 [32]) using the aug-cc-pVDZ basis set [33, 34]. Harmonic frequency calculations were performed to confirm the nature of the potential energy surface minima. Single-point energies were computed using the MP2/aug-cc-pVTZ level on the geometries that were optimized at the MP2/aug-cc-pVDZ level. The interaction energies of the complexes were then calculated as the

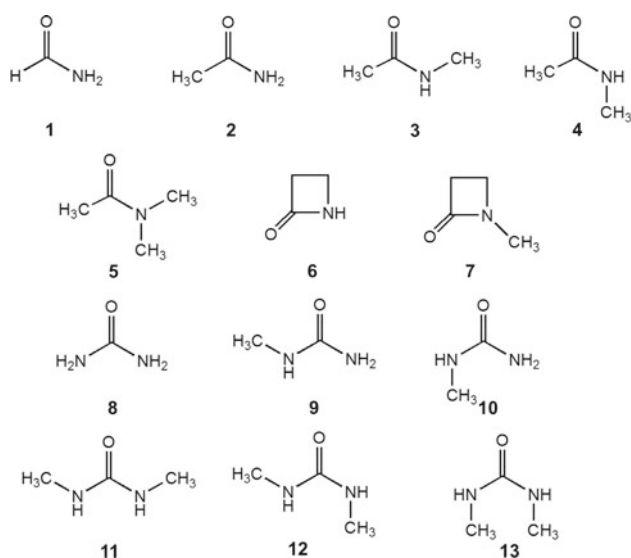


Fig. 1 Molecular structure of the molecules whose 1:1 complexes with CO_2 were analyzed in this work

difference between the energy of the complex and the sum of the energies of the relaxed isolated monomers. In a previous work [26], we showed that this computational scheme provides results close to the much more costly CCSD(T)/aug-cc-pVDZ calculations. Basis set superposition errors were estimated in the same work and were shown to be small; hence, they will not be calculated here. We also showed that the geometry of this type of complexes can be obtained through DFT calculations using the M06-2x [35] and wB97XD [36] functionals, although the results are not very accurate.

Natural bonding orbitals (NBO) calculations [37, 38] were performed (using SCF densities and MP2/aug-cc-pVDZ optimized geometries) to examine the electronic properties of the complexes, in particular to examine the nature of the interactions. All calculations were run using Gaussian 09 [39].

3 Results and discussion

3.1 Structures

We start the discussion by presenting a description of the structure of different types of complexes between the molecules that were considered in this study (Fig. 1) and a CO_2 molecule. We have limited the analysis to complexes of type I and III, according to the nomenclature proposed in our previous work [26], and to complexes of type IV, specific for amides and carbamides. These structures are summarized in Scheme 1. T-shaped complexes (type II in Ref. [26]) and structures involving only hydrogen bonds

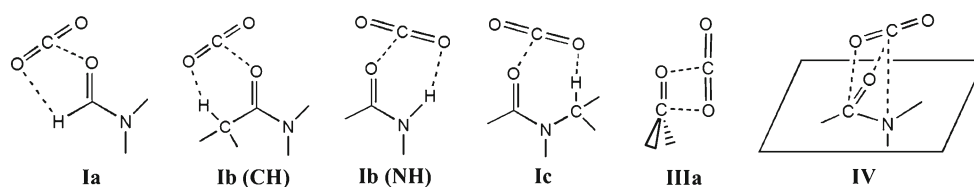
are also possible, but in principle, they should be less stable than I and have not been considered here.

As it has been already discussed [26–28], in complexes of type I, CO_2 behaves as a LA, whereas the carbonyl compound plays the role of a LB. Besides, a weak hydrogen bond is formed between an H atom on the molecule (in α or β position) and the O atom of CO_2 . In the present study, the Ia complex can only be found in the case of formamide and the Ib complex may involve a hydrogen atom attached to the N or C atoms. These two situations are indicated as Ib(NH) and Ib(CH), respectively. As shown below, in one asymmetric urea derivative (molecule 10), two distinct Ib(NH) complexes are possible; we distinguish the two of them by using the labels Ib(NH) and Ib(NH'). Complexes of type IIIa have a particular geometry in which four atoms form a roughly planar interaction site (a four-membered ring), and two kinds of LA–LB interactions are active, with CO_2 acting as either a donor or an acceptor of electron density. Complexes of type IV are reported here for the first time. They involve interactions between CO_2 and the π system of the amide/urea moiety, as described below.

The optimized geometries for the complexes that we treated are summarized in Fig. 2: for all reported minima, we obtained real frequencies only. We observe that in the case of formamide, only I type complexes could be found. This result agrees with what has been found in the case of aldehydes [26] and suggests that the out-of-plane structures are not stable when an H atom is directly attached to the carbonyl group. All complex types (I, III and IV) were found for the other compounds, apart from the following cases: a) no IIIa complexes were observed in acetamide or in urea derivatives having at least one N–H bond in the syn periplanar position with respect to the C=O bond, and b) no IV complexes were found with β -lactams 6 and 7.

3.2 Energies

In the following, we present an analysis of the relative stabilities of different complexes. The interaction energies calculated at the MP2/aug-cc-pVDZ level are shown in Table 1 together with the MP2/aug-cc-pVTZ single-point energies calculated on MP2/aug-cc-pVDZ optimized geometries. Although some slight differences can be observed, the general trends predicted by the two methods are in reasonable agreement. The interaction energies vary between -3.88 and -5.87 kcal/mol at the MP2/aug-cc-pVTZ level and between -3.33 and -6.79 kcal/mol at the MP2/aug-cc-pVDZ level. These values are comparable to those previously found for aldehydes, ketones and esters, though in some cases, the interaction energies are slightly higher (in absolute value). The largest interaction energy with CO_2 occurs for the IV(NCH₃) complex formed by



Scheme 1 Schematic representation of the interactions taking place in the different complexes studied in this work

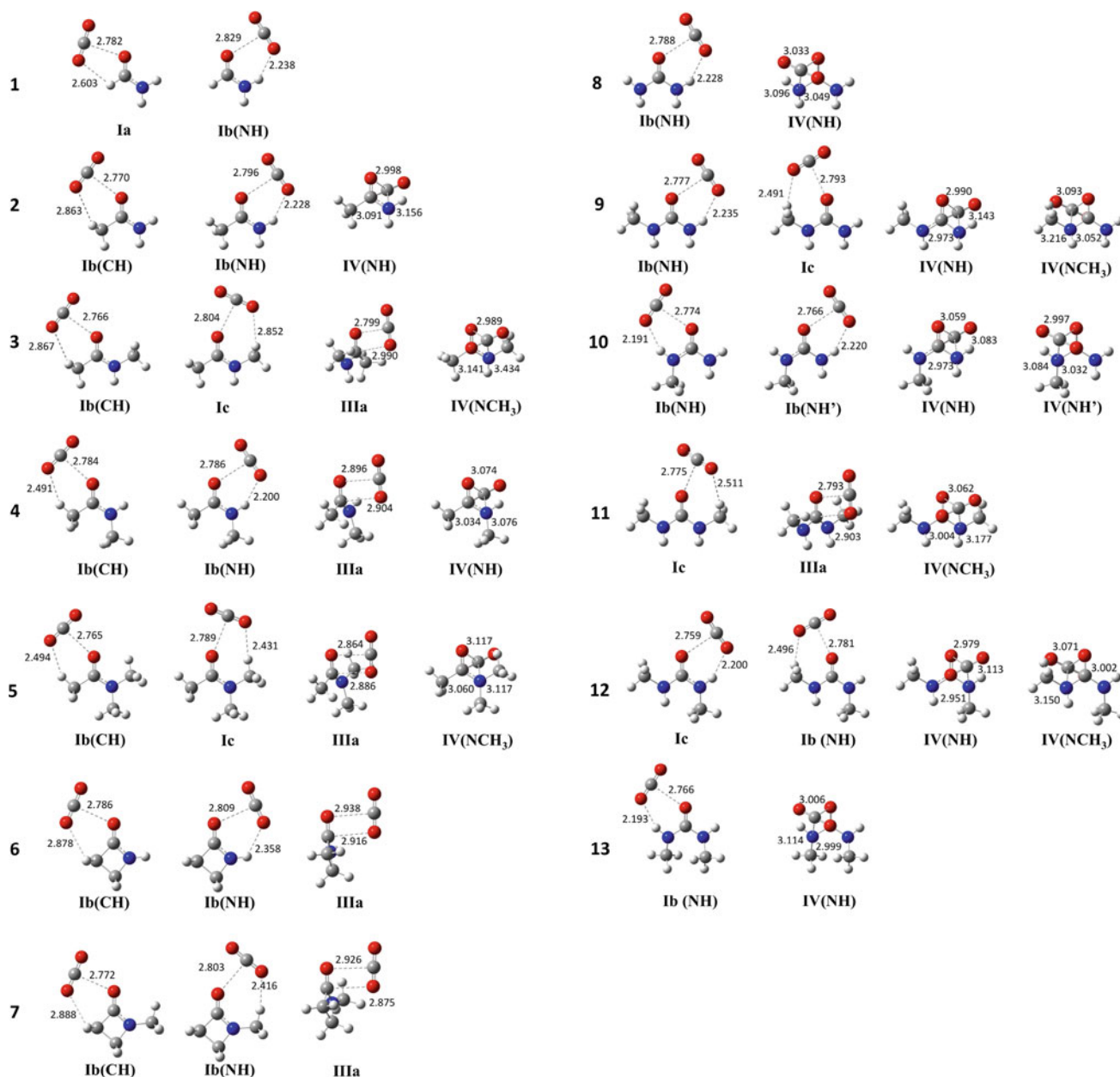


Fig. 2 Optimized structures (at the MP2/aug-cc-pVDZ level) for the complexes that were studied in this work. Distances characterizing the main interactions between the molecules shown in Fig. 1 and CO₂ are reported in Å

compound 11, that is *N,N'*-dimethylurea with both methyl groups in syn periplanar position with respect to C=O. We report as Supporting Information the interaction energies

corrected by the zero point energy (ZPE) contribution, enthalpies and entropies (MP2/aug-cc-pVDZ level) as obtained from the harmonic vibrational frequencies

Table 1 Calculated interaction energies (in kcal/mol) for the complexes in Fig. 2

Amides	Complex type	ΔE		Carbamides	Complex type	ΔE	
		DZ	TZ			DZ	TZ
1	Ia	-4.05	-3.88	8	Ib(NH)	-5.14	-5.01
	Ib(NH)	-4.93	-4.76		IV(NH)	-4.30	-3.78
2	Ib(NH)	-5.21	-5.01	9	Ib(NH)	-5.23	-5.09
	Ib(CH)	-4.20	-3.98		Ic	-4.23	-4.02
	IV(NH)	-4.27	-3.81		IV(NCH ₃)	-4.83	-4.19
3	Ib(CH)	-4.43	-4.16	10	IV(NH)	-5.06	-4.43
	Ic	-4.28	-4.06		Ib(NH)	-5.44	-5.30
	IIIa	-4.83	-4.29		Ib(NH')	-5.65	-5.46
	IV(NCH ₃)	-4.73	-4.09		IV(NH)	-5.18	-4.51
4	Ib(NH)	-5.49	-5.25	11	IV(NH')	-4.78	-4.24
	Ib(CH)	-4.39	-4.17		Ic	-5.52	-5.12
	IIIa	-4.74	-4.18		IIIa	-5.55	-4.89
	IV(NH)	-4.74	-4.16		IV(NCH ₃)	-6.79	-5.87
5	Ib(CH)	-4.56	-4.33	12	Ib(NH)	-5.74	-5.54
	Ic	-4.45	-4.18		Ic	-4.47	-4.26
	IIIa	-5.75	-4.99		IV(NCH ₃)	-5.81	-5.02
	IV(NCH ₃)	-5.45	-4.61		IV(NH)	-5.57	-4.87
6	Ib(NH)	-5.10	-4.84	13	Ib(NH)	-5.66	-5.44
	Ib(CH)	-4.55	-4.18		IV(NH)	-5.41	-4.74
	IIIa	-4.37	-3.90				
7	Ib(CH)	-4.55	-4.22				
	Ic	-4.73	-4.36				
	IIIa	-5.25	-4.53				

The labels DZ and TZ stand for the MP2/aug-cc-pVDZ and for the MP2/aug-cc-pVTZ//MP2/aug-cc-pVDZ calculations, respectively

analysis carried out at 298 K. The corresponding values for the acetone complexes are reported as a comparison. Note that the ZPE contribution is similar for all the complexes (1.0–1.5 kcal/mol) and does not affect the stability trends discussed below, which are based on electronic energies. Note also that the computed entropies are comparable to those reported for 1:1 complexes having similar interaction energies.

As a rule, we can say that carbamide-CO₂ complexes are slightly more stable than the amide-CO₂ ones. Indeed, for each carbamide-CO₂ complex, there is at least one arrangement for which the interaction energy is greater than (in absolute value) 5 kcal/mol, whereas the interaction energy in amide-CO₂ complexes is in general below that value (the exceptions are the 2 Ib(NH) and 4 Ib(NH) complexes that display interaction energies of -5.01 and -5.25 kcal/mol, respectively). Some other general trends are (1) whenever the Ib(NH) interaction type is possible for a given complex (either in amide or carbamide derivatives), such complex type is the most favorable one and (2) when the Ib(NH) interaction type is not possible, then the IIIa interaction type becomes the most favorable one

(except in 11 where, as said above, IV(NCH₃) leads to the largest interaction type in the whole series). The average interaction energy for Ib(NH) complexes is -5.17 kcal/mol, and for IIIa complexes -4.46 kcal/mol (similarly, one obtains average values of -3.88 kcal/mol for Ia, -4.17 kcal/mol for Ib(CH), -4.33 kcal/mol for Ic and -4.49 kcal/mol for IV complexes; the average energy, obtained by taking into account all the structures, is -4.56 kcal/mol).

3.3 NBO analysis

To investigate the nature of the interactions between CO₂ and the different molecules that we considered, and to connect the geometrical properties of the complexes with the electronic and energetic properties, we carried out natural bond orbital analysis using SCF densities and optimized geometries at the MP2/aug-cc-pVDZ level. In Table 2, we analyze the main contributions to donor-acceptor second-order energies, also providing the nature of the molecular orbitals involved in the interactions. The shape of the orbitals involved in all the complexes of 3 with

Table 2 NBO analysis: results obtained by using second-order perturbation theory to characterize intermolecular interactions

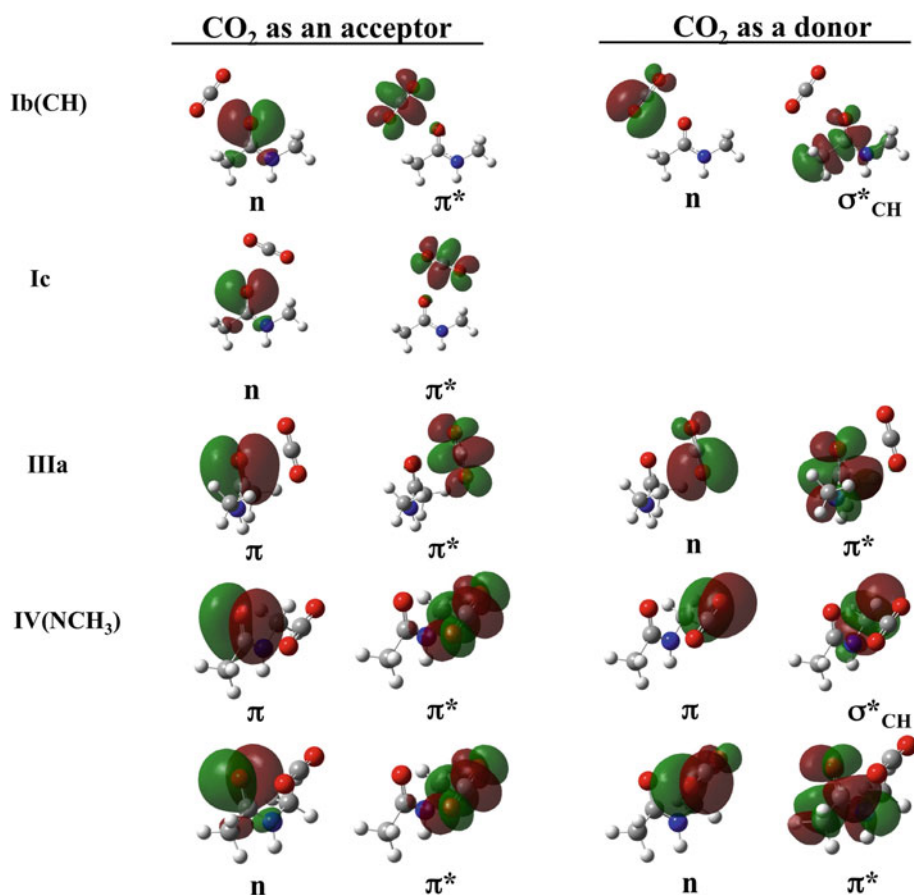
Complex	Donor/ acceptor	Orbitals	E ²	Complex	Donor/ acceptor	Orbitals	E ²			
1	Ia	Substrate/CO ₂	$n\pi^*$	1.86	8	Ib(NH)	Substrate/CO ₂	$n\pi^*$	1.54	
		CO ₂ /Substrate	$n\sigma_{CN^*}$	0.26			CO ₂ /Substrate	$n\sigma_{NH^*}$	1.99	
		CO ₂ /Substrate	$n\sigma_{CH^*}$	0.28			CO ₂ /Substrate	$n\sigma_{NH^*}$	1.62	
		CO ₂ /Substrate	$n\sigma_{CH^*}$	0.37			IV(NH)	Substrate/CO ₂	$\pi\pi^*$	0.49
Ib(NH)	Substrate/CO ₂	$n\pi^*$	1.39	Substrate/CO ₂	$n\pi^*$	0.46				
	CO ₂ /Substrate	$n\sigma_{NH^*}$	1.75	CO ₂ /Substrate	$n\pi^*$	0.86				
	CO ₂ /Substrate	$n\sigma_{NH^*}$	1.72	9	Ib(NH)	Substrate/CO ₂		$n\pi^*$	1.53	
2	Ib(NH)	Substrate/CO ₂	$n\pi^*$			1.53	CO ₂ /Substrate	$n\sigma_{NH^*}$	1.55	
		CO ₂ /Substrate	$n\sigma_{NH^*}$			1.55	CO ₂ /Substrate	$n\sigma_{NH^*}$	1.96	
		CO ₂ /Substrate	$n\sigma_{NH^*}$			1.96	Ic	Substrate/CO ₂	$n\pi^*$	0.99
Ib(CH)	Substrate/CO ₂	$n\pi^*$	1.76	CO ₂ /Substrate	$n\sigma_{CH^*}$	0.98				
	CO ₂ /Substrate	$n\sigma_{CH^*}$	0.23	IV(NCH ₃)	Substrate/CO ₂	$\pi\pi^*$		0.69		
IV(NH)	Substrate/CO ₂	$\pi\pi^*$	0.63		Substrate/CO ₂	$n\pi^*$		0.22		
	Substrate/CO ₂	$n\pi^*$	0.24		CO ₂ /Substrate	$n\pi^*$	0.87			
	CO ₂ /Substrate	$n\pi^*$	0.64		CO ₂ /Substrate	$n\sigma_{CH^*}$	0.48			
3	Ib(CH)	Substrate/CO ₂	$n\pi^*$	1.71	10	IV(NH)	Substrate/CO ₂	$\pi\pi^*$	0.78	
		CO ₂ /Substrate	$n\sigma_{CH^*}$	0.23			Substrate/CO ₂	$n\pi^*$	0.19	
	Ic	Substrate/CO ₂	$n\pi^*$	1.00			CO ₂ /Substrate	$n\pi^*$	1.23	
		IIIa	Substrate/CO ₂	$\pi\pi^*$			1.52	Ib(NH)	Substrate/CO ₂	$n\pi^*$
IV(NCH ₃)	CO ₂ /Substrate	$n\pi^*$	0.57	CO ₂ /Substrate	$n\sigma_{NH^*}$	2.40				
	Substrate/CO ₂	$\pi\pi^*$	0.96	CO ₂ /Substrate	$n\sigma_{NH^*}$	2.42				
	Substrate/CO ₂	$n\pi^*$	0.13	Ib(NH')	Substrate/CO ₂	$n\pi^*$	1.62			
4	Ib(NH)	CO ₂ /Substrate	$\pi\sigma_{CH^*}$		0.61	CO ₂ /Substrate	$n\sigma_{NH^*}$	1.66		
		CO ₂ /Substrate	$n\pi^*$		0.34	CO ₂ /Substrate	$n\sigma_{NH^*}$	2.06		
		Substrate/CO ₂	$n\pi^*$		1.58	IV(NH)	Substrate/CO ₂	$\pi\pi^*$	0.60	
Ib(CH)	CO ₂ /Substrate	$n\sigma_{NH^*}$	2.38	Substrate/CO ₂	$n\pi^*$		0.34			
	CO ₂ /Substrate	$n\sigma_{NH^*}$	2.38	CO ₂ /Substrate	$n\pi^*$		1.25			
	IIIa	Substrate/CO ₂	$n\pi^*$	1.46	IV(NH')		Substrate/CO ₂	$\pi\pi^*$	0.47	
CO ₂ /Substrate		$n\sigma_{CH^*}$	0.65	Substrate/CO ₂		$n\pi^*$	0.66			
CO ₂ /Substrate		$n\sigma_{CH^*}$	0.95	CO ₂ /Substrate		$n\pi^*$	0.64			
5	Ib(CH)	Substrate/CO ₂	$\pi\pi^*$	1.25		11	Ic	Substrate/CO ₂	$n\pi^*$	1.10
		CO ₂ /Substrate	$n\pi^*$	1.72	CO ₂ /Substrate			$n\sigma_{CH^*}$	0.94	
		CO ₂ /Substrate	$n\pi^*$	1.72	IIIa			Substrate/CO ₂	$\pi\pi^*$	1.03
	IV(NH')	Substrate/CO ₂	$\pi\pi^*$	0.55				CO ₂ /Substrate	$n\pi^*$	0.99
Substrate/CO ₂		$n\pi^*$	0.54	IV(NCH ₃)		Substrate/CO ₂	$\pi\pi^*$	0.79		
CO ₂ /Substrate		$n\pi^*$	0.92			Substrate/CO ₂	$n\pi^*$	0.22		
6	Ib(CH)	Substrate/CO ₂	$n\pi^*$		1.44	CO ₂ /Substrate	$n\pi^*$	1.03		
		CO ₂ /Substrate	$n\sigma_{CH^*}$		0.65	CO ₂ /Substrate	$n\pi^*$	0.45		
		CO ₂ /Substrate	$n\sigma_{CH^*}$	0.98	12	Ib(NH)	Substrate/CO ₂	$n\pi^*$	1.63	
Ic	Substrate/CO ₂	$n\pi^*$	1.08	CO ₂ /Substrate			$n\sigma_{NH^*}$	2.32		
	CO ₂ /Substrate	$n\sigma_{CH^*}$	1.42	CO ₂ /Substrate			$n\sigma_{NH^*}$	2.36		
	IIIa	Substrate/CO ₂	$\pi\pi^*$	1.41			Ic	Substrate/CO ₂	$n\pi^*$	1.09
IV(NCH ₃)	CO ₂ /Substrate	$n\pi^*$	1.08	CO ₂ /Substrate	$n\pi^*$	0.96				
	Substrate/CO ₂	$\pi\pi^*$	0.58	IV(NCH ₃)	Substrate/CO ₂	$\pi\pi^*$		0.72		
	Substrate/CO ₂	$n\pi^*$	0.54		Substrate/CO ₂	$n\pi^*$		0.31		
CO ₂ /Substrate	$n\pi^*$	0.70	CO ₂ /Substrate		$n\pi^*$	1.00				
CO ₂ /Substrate	$\pi\sigma_{CH^*}$	0.24	6		Ib(NH)	CO ₂ /Substrate	$\pi\sigma_{CH^*}$	0.42		
7	Ib(NH)	Substrate/CO ₂		$n\pi^*$		1.58	IV(NH)	Substrate/CO ₂	$\pi\pi^*$	0.65
		CO ₂ /Substrate		$n\sigma_{NH^*}$		1.65				

Table 2 continued

Complex	Donor/acceptor	Orbitals	E^2	Complex	Donor/acceptor	Orbitals	E^2	
Ib(CH)	CO ₂ /Substrate	$n\sigma_{\text{NH}^*}$	1.25	13	Ib(NH)	Substrate/CO ₂	$n\pi^*$	0.46
	Substrate/CO ₂	$n\pi^*$	1.58			CO ₂ /Substrate	$n\pi^*$	1.03
IIIa	CO ₂ /Substrate	$n\sigma_{\text{CC}^*}$	0.48	IV(NH)	Substrate/CO ₂	$n\pi^*$	1.61	
	Substrate/CO ₂	$\pi\pi^*$	1.08		CO ₂ /Substrate	$n\sigma_{\text{NH}^*}$	2.31	
7	CO ₂ /Substrate	$n\pi^*$	1.65	IV(NH)	Substrate/CO ₂	$n\sigma_{\text{NH}^*}$	2.46	
	Substrate/CO ₂	$n\pi^*$	1.80		Substrate/CO ₂	$\pi\pi^*$	0.75	
Ic	CO ₂ /Substrate	$n\sigma_{\text{CC}^*}$	0.48	Substrate/CO ₂	$n\pi^*$	0.35	1.14	
	Substrate/CO ₂	$n\pi^*$	1.07	CO ₂ /Substrate	$n\pi^*$			
IIIa	CO ₂ /Substrate	$n\sigma_{\text{CH}^*}$	1.25					
	Substrate/CO ₂	$\pi\pi^*$	1.14					

The second-order energetic contributions (E^2) to the most important donor/acceptor interactions are reported in kcal/mol

Fig. 3 Shape of the natural molecular orbitals involved in the main donor–acceptor intermolecular interactions of different type of structures for all the complexes formed by *N*-methylacetamide with CO₂



CO₂ is represented in Fig. 3. For simplicity, the amide or carbamide derivative interacting with CO₂ will be referred to as “substrate”.

In the case of complexes I and III, our results generalize what we had already found for aldehydes (only I complexes are formed in that case), ketones and esters.

In complexes of type I, the main interactions are (1) a typical LB–LA donor–acceptor interaction, in which the

n orbital of the carbonyl group of the substrate interacts with the π^* orbital of CO₂ and (2) one or two interactions in which the in-plane n orbitals of CO₂ interact with σ^* orbitals of the substrate. In the case of the Ia complex, two different σ^* orbitals are involved, one for the C–H bond and one for the C–N bond. For Ib complexes, we need to distinguish between Ib(CH) and Ib(NH) interactions. In the former case, only the σ^* orbital of a C–H bond is involved

but for the four-membered cyclic molecules 6 and 7, where we interestingly observe a weak interaction involving the σ^* orbital for the C–C bond (note in Fig. 2 that the C–H bond in 6 and 7 is out-of-plane). In Ib(NH) complexes, we observe two interactions between n orbitals of CO₂ and the σ^* orbital of the N–H bond of the substrate. Finally, for Ic complexes, the σ^* orbital involved is that of the C–H bond of the *N*-methyl group. The interactions in which CO₂ behaves as an acceptor and those in which it behaves as a donor have usually the same order of magnitude, with a few exceptions in complexes Ib(NH) of urea derivatives, where the two $n\sigma^*$ interactions related to the O··H–N hydrogen bond have, not surprisingly, a much larger contribution. This fact is connected to the acidity of the NH amide proton and explains the large stability of the Ib(NH) structures discussed above.

In IIIa complexes, we observe (1) a contribution due to the π orbital of the substrate interacting with the π^* orbital of CO₂ and (2) a contribution due to the n orbital of CO₂ interacting with a π^* orbital of the substrate. In the latter case, the CO₂ molecule behaves as a Lewis base.

Let us now consider IV complexes, which are specifically formed in the case of amides and carbamides. As shown in Table 2: (1) both a π and an n orbital localized on the carbonyl group of the substrate can interact with a π^* orbital of CO₂, and (2) an n orbital of CO₂ interacts with a π^* orbital of the substrate in all IV complexes; it is worth emphasizing that this π^* orbital has a substantial contribution from the p_z orbital on the N atom. In addition, in the case of IV(NCH₃) complexes (i.e., when a methyl group is in the syn periplanar position with respect to the carbonyl group), there is a weak hydrogen bond interaction that involves a π orbital of CO₂ and the C–H σ^* orbital of the *N*-methyl group of the substrate.

It is apparent now to what extent the presence of the a nitrogen atom(s) in amides and carbamides influences the interaction of carbonyl groups with carbon dioxide. Compared to carbonyl compounds in aldehydes, ketones or esters, the 1:1 complexes with CO₂ can be significantly stabilized due to the interaction of CO₂ with the acidic H–N protons. However, this is not the only important feature, and in fact, the presence of the N atom, through its participation to the delocalized π system, allows for a direct interaction with CO₂. In the latter case, CO₂ behaves as a LB, one of its n orbitals donating electron charge to a delocalized π^* antibonding orbital in the amide/urea unit.

4 Conclusions

The study reported in this paper shows that amide and carbamide derivatives have significant affinity for carbon dioxide. They therefore appear as suitable and promising

functionalizing groups for increasing the solubility of large molecules in supercritical CO₂. The case of amides is particularly interesting because our results suggest that the interactions of CO₂ with the backbone of peptides and proteins might provide a substantial contribution to the stabilization of such systems in supercritical CO₂, a topic that has high biotechnological relevance.

Moreover, the results reported above confirm and extend the previous conclusion obtained in the study of aldehydes, ketones and esters, stating that, beyond its usual Lewis acid character, CO₂ may behave as a Lewis base when it interacts with carbonyl compounds. In the case of amides and carbamides, we have seen that such an interaction is characterized by the participation of a π^* orbital delocalized over the O, C and N atoms (structures IV). However, when the amide or carbamide derivative bears an NH proton in the syn periplanar position with respect to the carbonyl group, the main interaction corresponds to an in-plane arrangement (structures Ib(NH)) in which there is cooperativity between the usual LA(CO₂)–LB(carbonyl compound) interaction and a hydrogen bond involving the acidic N–H proton. The fact that CO₂ may behave as both a Lewis acid and a Lewis base suggests that cooperative interactions, already pointed out in the case of 1:1 complexes (see the Introduction), might play a role in the case of 1:2 complexes. This is an important topic that needs to be addressed, and further work is being done in this direction.

The findings reported in this work open new perspectives in the design of green chemical procedures using supercritical CO₂ as a solvent, so far a challenging task due to solubility limitations.

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