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Reaction of R_F-palmitic acid-F_{13} with dicyclohexylcarbodiimide

Gerald W. Buchanan [a,*], Majid F. Rastegar [a], Gary Enright [b]

[a] Ottawa-Carleton Chemistry Institute, Department of Chemistry, Carleton University, Ottawa, Canada K1S 5B6
[b] Steacie Institute for Molecular Sciences, National Research Council, Ottawa, Canada K1A 0R6

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Abstract

The 1,3-dicyclohexylcarbodiimide (DCC) adduct of R_F-palmitic acid-F_{13} **1** has been synthesized and characterized. The X-ray crystal structure shows that the product arises from an *O*- to *N*-acyl migration of an initially formed *N*,*N*′-dicyclohexyl-*O*-R_F-palmitoyl-F_{13}-isourea **2** to give 1-R_F-palmitoyl-F_{13}-1,3-dicyclohexylurea **3**. X-ray data for an R_F-palmitic acid-F_{13} unit are reported for the first time. The product of the reaction of DCC with palmitic acid is also the urea derivative which has been characterized by IR and NMR methods.

Keyword : Fluorinated palmitic acid derivative

1. Introduction

Carboxylic acids are known to react with carbodiimides such as 1,3-dicyclohexylcarbodiimide (DCC) to give acylisourea intermediates which subsequently rearrange to urea derivatives [1]. The bulky DCC group can be effectively employed to function as an end cap for a variety of rotaxanes [2] and the reagent is particularly useful for the acylation step in the synthesis of polypeptides from amino acids [3,4]. The acyl group is highly reactive in this environment because cleavage of the acyl-oxygen bond converts the C=N bond of the isourea to a more stable C=O moiety [5–7]. Although this *O*-acyl to *N*-acyl migration has been reported several times [5–9] little detailed structural information on the products has been available due to the paucity of X-ray crystallographic data. Interpretation of ^{13}C NMR data for these compounds is not straightforward, due to the possibility of geometrical isomers about the C=N in the isoureas [8] and restricted rotation about amide type bonds in the ureas. The literature contains one clear example of an acylisourea converting to a urea derivative [10]. In this case, ferrocene carboxylic acid reacts with DCC in THF at room temperature to give *N*,*N*′-dicyclohexyl-*O*-ferrocenoylisourea, which can be converted to *N*,*N*′-dicyclohexyl-*N*-ferroceneoylurea in dioxane at reflux temperature. Unfortunately no ^{13}C NMR data were included for either the original or rearranged products and characterization was made using IR and ^{1}H NMR only.

During the course of our attempted synthesis of glycerol tripalmitate-F_{39} [11] we had the occasion to react R_F-palmitic acid-F_{13} **1** with DCC. The X-ray crystal structure of the resulting product has been determined and is the first available X-ray crystal structure of this type of urea derivative. Further characterization via ^{13}C NMR and IR spectroscopic methods is also included. In order to examine the influence of fluorination on the reaction, results for palmitic acid itself are compared to those for those for the terminally perfluorinated system.

2. Results and discussion

The structure of the initially formed intermediate in the reaction of **1** with DCC is shown below. In this isourea type structure **2**, the two nitrogen environments would be rendered equivalent via a 1,3 proton shift (i.e. a tautomerisation) which, by analogy with imidazole, should be fast on the NMR timescale. This would lead to the expectation that there should only be one ^{13}C NMR chemical shift for cyclohexyl carbons bonded to nitrogen in the region of 50–60 ppm. However, this is not the case, indeed there are two resonances of equal intensity at 49.8 and 55.1 ppm. These chemical shifts can be compared to that observed for the C1 of cyclohexyl amine [12] at 51.4 ppm. As expected for the rearranged product there are two chemical shifts in the carbonyl region of the ^{13}C spectrum, with the amide

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[*] Corresponding author. Tel.: +1 613 520 3840.
E-mail address: gerald_buchanan@carleton.ca (G.W. Buchanan).

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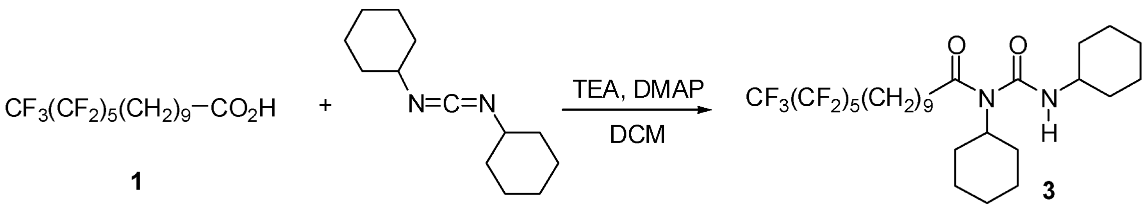
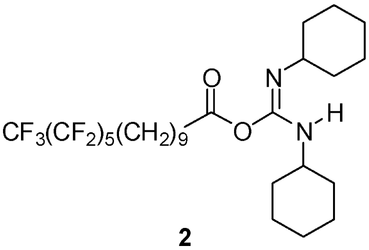
type carbon (C14) being the most deshielded at 172.8 ppm. The urea type carbonyl (C7) resonates at 154.0 ppm, which is consistent with its lower double bond character due to the influence of two directly bonded nitrogen atoms. The total number of observed ^{13}C resonances is 25, indicating that there is no restricted rotation about bonds involving C7 or C14 on the NMR timescale at room temperature.

The IR spectrum of the adduct shows strong absorptions at 1658 and 1698 cm^{-1} which are essentially identical to the values reported for the product of DCC with acetic acid [5] in which rearrangement to the acetyldicyclohexylurea has occurred. These findings support the argument that the isolated product is in fact the rearranged product **3**, which is now confirmed by X-ray crystallography.

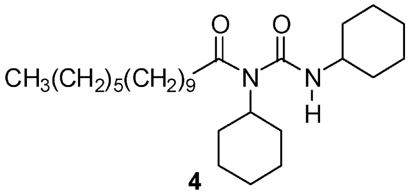
For palmitic acid itself, we find similar results. Indeed the dicyclohexylurea system **4** has been obtained in good yield ruling out the possibility that the influence of the electronegative fluorine atoms in the chain is increasing the propensity of the molecule to undergo the *O*-acyl to *N*-acyl migration.



1 **3**



2



4

2.1. X-ray crystallographic structure of 3

The ORTEP structure of **3** is depicted below along with the Crystallographic data and structure refinement in Table 1. Bond lengths, bond angles, anisotropic displacement factors, hydrogen coordinates and torsion angles for **3** are presented in Tables 2–6, respectively and are available as Supplementary Data. The conformation of the $\mathrm{R_F}$-palmitic acid portion of the adduct is of particular interest, since no literature reports of fluorinated palmitate X-ray structures have been published. In the non-fluorinated part of the chain (C15–C23) the conformation is almost perfectly staggered, with all C–C–C–C angles near 180°. This geometry is somewhat altered in the fluorinated portion of the chain (C24–C29), with typical C–C–C–C torsion angles in the range of 160–165°. There is some evidence for a slight helicity in this part of the chain and the structure is similar to that observed in the fluorinated portion of hydrated bis(*n*-perfluoroalkyl)phosphinic acids [13].

Another point of interest are the bond angles involving the amide and urea type carbon oxygen double bonds. For the amide carbon (C14) the three bond angles involving this carbon are 121.4°, 121.4° and 117.2° with the N1–C14–C15 angle being the smallest. In the case of the urea type carbon (C7) the N2–C7–N1 angle is 112.8°, while the two angles involving the oxygen atom are 121.4° and 125.8°.

3. Experimental

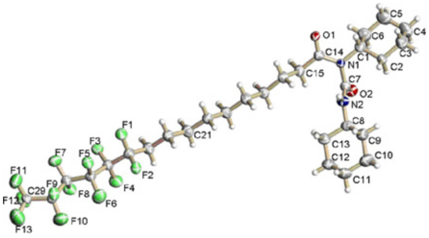
$\mathrm{R_F}$-palmitic acid-$\mathrm{F_{13}}$ **1** was prepared as described previously [14].

Compound **3** was prepared as follows: Under an argon atmosphere, 0.98 g (2 mmol) of **1**, 0.36 mL (2.6 mmol) triethyl amine and 24.4 mg (0.2 mmol) of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) were added to an oven dried 50 mL round bottom flask and dissolved in 25 mL of anhydrous dichloromethane (DCM). The reaction mixture was stirred for 15 min in an ice bath. Subsequently to this was added dropwise over a period of 10 min a solution of dicyclohexylcarbodiimide (DCC), 0.41g (2 mmol) in 10 mL of anhydrous DCM. The reaction mixture was stirred for 4 h in the ice bath and then overnight at room temperature. The solvent was then removed by rotary evaporation and the crude product was purified using column chromatography on silica gel with 90:10 hexane:ethylacetate as eluent. The main component was a white solid which was dissolved in a minimal amount of toluene and treated with activated carbon. Upon gradual cooling of the filtrate 0.63 g (67% yield) of colorless crystals were obtained, mp 84–5 °C.

^{1}H NMR of **3**: 5.40 (d, 1H), 3.75 (m, 1H), 2.06 (t, $J = 7.6$, 2H), 1.98 (m, 2H), 1.82 (m, 3H), 1.60 (m, 10H), 1.23 (m, 18H), 1.04 (m, 4H). ^{13}C NMR of **3**: 172.8, 154.0, 120.8 (m), 118.3 (m), 115.7 (m), 113.6 (m), 111.3 (m), 108.6 (m), 55.1, 49.8, 35.5, 32.5, 30.7, 30.7 (t, $J = 22.3$), 29.2, 29.1 (intensity 2), 28.9, 26.1 (intensity 2), 25.4, 25.3, 25.2, 24.6, 19.9. Mass spec. $C_{29}H_{41}N_2F_{13}O_2$; electrospray ionization with K^+: parent ion at $m/z = 734.6$, arising from $696.6 + 39 - 1$. Anal. calcd. for $C_{29}H_{41}N_2F_{13}O_2$: C 50.00, H 5.93, N 4.02, F 35.46, O 4.59. Found: C 50.22, H 6.00, N 3.99, F 34.96.

Compound **4** was prepared as follows: Under an argon atmosphere, 1.024 g (4 mmol) of palmitic acid, 0.36 mL

Table 1
Crystal data and structure refinement for **3**



Identification code	**3**
Empirical formula	$C_{29}H_{41}F_{13}N_2O_2$
Formula weight	696.64
Temperature	125(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P12(1)/c1$
Unit cell dimensions	$a = 15.6192(12)$ Å, $\alpha = 90°$; $b = 9.2323(7)$ Å, $\beta = 108.3770(10)°$; $c = 23.9898(18)$ Å, $\gamma = 90°$
Volume	3282.9(4) Å^3
Z	4
Density (calculated)	1.409 Mg/m^3
Absorption coefficient	0.138 mm^{-1}
$F(0\,0\,0)$	1448
Crystal size	0.450 mm × 0.30 mm × 0.30 mm
Theta range for data collection	1.37–29.60°
Index ranges	$-21 \leq h \leq 21$, $-12 \leq k \leq 12$, $-33 \leq l \leq 33$
Reflections collected	39,470
Independent reflections	9141 [R(int) = 0.0290]
Completeness to $\theta = 29.60°$	99.0%
Absorption correction	Multiscan
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	9141/0/579
Goodness-of-fit on F^2	1.029
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0386$, $wR_2 = 0.0984$
R indices (all data)	$R_1 = 0.0613$, $wR_2 = 0.1158$
Largest diff. peak and hole	0.468 and −0.245 einstein Å^{-3}

(5.2 mmol) triethyl amine and 48.8 mg (0.4 mmol) DMAP were added to an oven dried 100 mL round bottom flask and dissolved in 50 mL of anhydrous $CHCl_3$. This mixture was stirred for 15 min at 0 °C and to this was added over 10 min a solution of DCC (0.99 g, 4.4 mmol) in anhydrous $CHCl_3$. The reaction mixture was stirred for 4 h in an ice bath and overnight at room temperature. Subsequently the solvent was removed by rotary evaporation and the crude product was purified using column chromatography on silica gel with 90:10 hexane:ethylacetate as eluent. The yield of **4** as a white solid, mp 64–66 °C was 1.45 g (78.3%).

^{1}H NMR of **4**: 7.20 (bs, 1H), 3.85 (m, 1H), 3.63 (m, 1H), 2.35 (t, $J = 7.6$, 2H), 1.75 (m, 12H), 1.21 (m, 34H), 0.83 (t, 6.6, 3H). ^{13}C NMR of **4**: 174.0, 154.1, 56.0, 49.7, 35.9, 32.7, 31.9, 30.9 (intensity 2), 29.8 (intensity 2), 29.7 (intensity 2), 29.6, 29.5, 29.4, 29.3, 29.2, 26.4 (intensity 2), 25.5 (intensity 2), 25.3, 24.7, 22.7, 14.1. Mass spec. $C_{29}H_{54}N_2O_2$; electron impact predicted m/z for parent ion at 462.7, obsd. $M - 1$ at 461.7. Anal. calcd. for $C_{29}H_{54}N_2O_2$: C 75.27, H 11.76, N 6.05, O 6.91. Found: C 75.41, H 11.63, N 5.99, O 6.97.

X-ray crystallographic measurements and structure refinement details are given along with Supplementary Data. The complete set of X-ray data have been placed in the International Data Base, reference number CCDC 644471.

Elemental analyses were carried out by Canadian Microanalytical Service Ltd. Delta B.C. Canada.

4. Conclusions

^{13}C NMR and X-ray crystallographic analysis indicates that the reaction of fluorinated and non-fluorinated fatty acids with DCC yields rearranged urea derivatives exclusively.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2007.05.005.

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