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NMR Chemical Shifts of Trace Impurities: Industrially Preferred Solvents Used in Process and Green Chemistry

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Supporting Information

ABSTRACT: The ^{1}H and ^{13}C NMR chemical shifts of 48 industrially preferred solvents in six commonly used deuterated NMR solvents ($CDCl_3$, acetone-d_6, DMSO-d_6, acetonitrile-d_3, methanol-d_4, and D_2O) are reported. This work supplements the compilation of NMR data published by Gottlieb, Kotlyar, and Nudelman (*J. Org. Chem.* **1997**, *62*, 7512) by providing spectral parameters for solvents that were not commonly utilized at the time of their original report. Data are specifically included for solvents, such as 2-Me-THF, *n*-heptane, and *iso*-propyl acetate, which are being used more frequently as the chemical industry aims to adopt greener, safer, and more sustainable solvents. These spectral tables simplify the identification of these solvents as impurities in NMR spectra following their use in synthesis and workup protocols.

■ INTRODUCTION

Over the past decade, there has been an increasing focus on the application of green chemistry principles throughout the chemical industry. A key component in the development of sustainable chemical processes is solvent, which constitutes approximately half of the mass used in the manufacture of active ingredients.[1] Further emphasizing the importance of solvent choice, one of the 12 Principles of Green Chemistry outlined by Anastas and Warner[2] specifically focuses on the use of safer solvents whenever possible. The implications of solvent selection are also aligned with those principles that encourage the use of more benign chemicals and renewable feedstocks. For example, bioderived solvents, or those that have life cycle advantages, can offer sustainability benefits over more conventional solvents.[3] Several pharmaceutical companies have published solvent selection guides to enable chemists to choose more sustainable solvents, with an emphasis on safety, health, and environmental impact.[4] In an attempt to align the recommendations of the various institutions and encourage the incorporation of these industrially preferred solvents into chemical research, a comprehensive evaluation of all of the solvents was published by the Innovative Medicines Initiative (IMI)−CHEM21[5] in 2014.[6]

Since their publication in 1997, the tables of chemical shifts found in *NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities* by Gottlieb, Kotlyar, and Nudelman have been an invaluable resource for synthetic chemists to identify residual solvents, e.g., Et_2O or THF, in research samples.[7] An expansion of these data tables to include gases and deuterated solvents commonly used in organometallic chemistry was published in 2010.[8] However, several solvents, such as 2-Me-THF, *n*-heptane, and *iso*-propyl acetate, were not widely employed at the time of the original publication but have since been recommended in several solvent selection guides based on their improved safety, sustainability, and/or environmental properties. For example, these recommended solvents often have higher flash points, making them more amenable to chemical processes. One shortcoming, however, is that this reduced volatility can make the removal of residual amounts of these solvents more difficult. In addition, the structures of many of these preferred solvents give rise to complex NMR spectra that complicate the assignment of minor impurity resonances. To simplify the identification of these solvents in NMR spectra and facilitate their adoption into chemical processes, we have compiled ^{1}H and ^{13}C NMR data for 48 solvents discussed in the CHEM21 solvent selection guides.[6,9] Complete NMR spectral parameters for 29 of these solvents have not been previously reported. The compiled data provided herein will serve as a practical resource when these newer, more preferred solvents are encountered as residual impurities in NMR spectra and, in turn, further advance green chemistry initiatives.

■ EXPERIMENTAL SECTION

All materials were obtained from commercial sources. Deuterated solvents (containing 0.05 vol % tetramethylsilane, TMS) were purchased from Cambridge Isotope Laboratories. Acetonitrile-d_3 (containing 1 vol % TMS) was obtained from Acros Organics. D_2O (0.05 wt % 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt) was purchased from Aldrich. NMR spectra were obtained using a Bruker AVANCE 400 MHz spectrometer, operating at 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C). ^{13}C{^{1}H} NMR spectra were obtained using composite pulse decoupling. Using the procedure described in the original publication,[7] stock solutions of mixtures of impurities were prepared and analyzed by NMR. Due to the spectral complexity of many of these solvents, the analysis was limited to solvent pairs to minimize spectral overlap and avoid ambiguous assignments. Pairs were chosen by consideration of reactivity

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Table 1. ^{1}H NMR Data

		proton	mult, J	$CDCl_3$	acetone-d_6	DMSO-d_6	CD_3CN	CD_3OD	D_2O
solvent residual peak				7.26	2.05	2.50	1.94	3.31	4.79
water	▲	H_2O	s	1.56	2.84	3.33	2.13	4.87	-
acetic acid [a]	▲	CH_3	s	2.10	1.96	1.91	1.96	1.99	2.08
acetic anhydride	▲	CH_3	s	2.23	2.21	2.22	2.18	-[b]	-[b]
acetone [a]	▲	CH_3	s	2.17	2.09	2.09	2.08	2.15	2.22
acetonitrile [a]	▼	CH_3	s	2.10	2.05	2.07	1.96	2.03	2.06
iso-amyl acetate	▲	OCH_2	t, 6.8	4.10	4.05	4.02	4.05	4.09	4.14
		CH_3CO	s	2.05	1.97	1.99	1.97	2.01	2.07
		CH	nonet, 6.7	1.68	1.69	1.64	1.67	1.69	1.67
		$\mathit{CH_2}CH$	q, 6.9	1.52	1.50	1.45	1.49	1.51	1.53
		$(CH_3)_2$	d, 6.6	0.92	0.91	0.88	0.91	0.93	0.89
iso-amyl alcohol	▲	$\mathit{CH_2}OH$	td, 6.8, 5.2	3.68, t (6.8)	3.56 [3.55, t][c]	3.41	3.51	3.57, t (6.9)	3.64, t (6.8)
		OH	t, 5.2	-	3.34	4.29	2.40	-	-
		CH	nonet, 6.7	1.72	1.73	1.65	1.67	1.71	1.67
		$\mathit{CH_2}CH$	q, 6.8	1.47	1.39	1.31	1.37	1.42	1.44
		CH_3	d, 6.7	0.92	0.89	0.85	0.89	0.91	0.90
anisole	▲	CH (3,5)	m	7.32-7.27	7.31-7.25	7.31-7.26	7.32-7.27	7.28-7.22	7.40, t (8.0)[d]
		CH (2,4,6)	m	6.97-6.89	6.96-6.89	6.94-6.90	6.96-6.90	6.92-6.87	7.09-7.03[d]
		OCH_3	s	3.81	3.78	3.75	3.77	3.77	3.85[d]
benzyl alcohol	▲	CH	m	7.38-7.28	7.37-7.29	7.36-7.28	7.37-7.30	7.36-7.30	7.47-7.37
		CH	m	7.38-7.28	7.25-7.20	7.25-7.20	7.29-7.23	7.26-7.22	7.47-7.37
		CH_2	d, 5.9	4.71	4.63 [4.62, s][c]	4.49	4.57	4.59, s	4.65, s
		OH	t, 5.9	1.64	4.16	5.16	3.14	-	-
n-butanol	▲	$\mathit{CH_2}OH$	td, 6.5, 5.3	3.65, t (6.7)	3.53 [3.52, t][c]	3.38	3.48	3.54, t (6.5)	3.61, t (6.6)
		$\mathit{CH_2}CH_2OH$	m	1.60-1.52	1.51-1.44	1.43-1.25	1.49-1.42	1.55-1.47	1.57-1.50
		$\mathit{CH_2}CH_3$	m	1.44-1.35	1.41-1.32	1.43-1.25	1.39-1.29	1.43-1.33	1.40-1.30
		OH	t, 5.3	1.20, br s	3.35	4.31	2.43	-	-
		CH_3	t, 7.3	0.94	0.90	0.86	0.91	0.93	0.91
iso-butanol	▲	CH_2	dd, 6.5, 5.5	3.41	3.29	3.15	3.25	3.31-3.29, m	3.38, d (6.6)
		CH	nonet, 6.6	1.77	1.68	1.60	1.66	1.70	1.75
		OH	t, 5.5	1.30	3.45	4.40	2.50	-	-
		CH_3	d, 6.7	0.92	0.87	0.82	0.86	0.90	0.89
tert-butanol	▲	CH_3	s	1.27	1.18 [1.18][c]	1.11	1.17	1.22	1.25
		OH	s	-	3.22	4.18	2.39	-	-
n-butyl acetate	▲	OCH_2	t, 6.7	4.07	4.02	3.99	4.02	4.05	4.12
		CH_3CO	s	2.05	1.97	1.99	1.97	2.01	2.09
		$OCH_2\mathit{CH_2}$	m	1.64-1.57	1.62-1.55	1.57-1.50	1.61-1.54	1.64-1.57	1.67-1.60
		$\mathit{CH_2}CH_3$	m	1.43-1.34	1.42-1.33	1.37-1.27	1.41-1.32	1.44-1.34	1.42-1.33
		$CH_2\mathit{CH_3}$	t, 7.4	0.94	0.92	0.89	0.92	0.94	0.91
iso-butyl acetate	▲	CH_2	d, 6.7	3.85	3.81	3.79	3.81	3.84	3.91
		CH_3CO	s	2.06	1.99	2.01	1.99	2.03	2.11
		CH	nonet, 6.7	1.92	1.89	1.87	1.90	1.92	1.94
		$(CH_3)_2$	d, 6.7	0.93	0.91	0.88	0.91	0.93	0.93
chlorobenzene	▼	CH	m	7.36-7.22	7.42-7.31	7.45-7.32	7.41-7.29	7.37-7.25	7.46-7.33
cyclohexane [a]	▼	CH_2	s	1.43	1.43	1.40	1.44	1.45	-
cyclohexanone [a]	▲	CH_2 (2,6)	t, 7	2.33	2.27	2.25	2.27	2.34	2.40
		CH_2 (3,5)	m	1.86-1.84	1.83-1.79	1.78-1.74	1.84-1.79	1.87-1.85	1.90-1.85
		CH_2 (4)	m	1.73-1.71	1.74-1.70	1.66-1.64	1.72-1.67	1.76-1.74	1.75-1.70
cyclopentyl methyl ether (CPME)	▼	CH	m	3.82-3.78	3.77-3.73	3.76-3.71	3.78-3.74	3.85-3.80	3.99-3.94
		OCH_3	s	3.28	3.19	3.15	3.19	3.26	3.30
		CH_2	m	1.74-1.50	1.72-1.44	1.67-1.42	1.70-1.48	1.77-1.50	1.86-1.51
p-cymene (4-*iso*-propyltoluene)	▼	ArH	m	7.14-7.09	7.13-7.07	7.12-7.07	7.14-7.09	7.09-7.04	-
		$\mathit{CH}(CH_3)_2$	sept, 6.9	2.87	2.85	2.83	2.86	2.83	-
		Ar-CH_3	s	2.32	2.27	2.25	2.28	2.27	-
		$(CH_3)_2$	d, 6.9	1.24	1.20	1.17	1.20	1.21	-
dichloromethane [a]	▼	CH_2	s	5.30	5.63	5.76	5.44	5.49	-
dimethyl carbonate [a]	▲	CH_3	s	3.79	3.72	3.69	3.72	3.74	3.69
dimethyl sulfoxide [a]	▼	CH_3	s	2.62	2.52	2.54	2.50	2.65	2.71
DMPU [e]	▼	NCH_2	m	3.25-3.22	3.25-3.22	3.20-3.17	3.22-3.19	3.30-3.27	3.30-3.27
		NCH_3	s	2.92	2.81	2.75	2.81	2.88	2.86
		CH_2	m	2.00-1.94	1.97-1.92	1.90-1.84	1.94-1.88	2.00-1.94	1.98-1.92
ethanol	▲	CH_2	qd, 7.0, 5.2	3.72, q (7.0)	3.57 [3.57, q][c]	3.44	3.54	3.60, q (7.1)	3.66, q (7.1)
		CH_3	t, 7.0	1.24	1.12 [1.12][c]	1.06	1.11	1.17	1.19
		OH	t, 5.2	1.42, br s	3.39	4.35	2.47	-	-
ethyl acetate [a]	▲	CH_3CO	s	2.05	1.97	1.99	1.97	2.01	2.07
		$\mathit{CH_2}CH_3$	q, 7	4.12	4.05	4.03	4.06	4.09	4.14
		$CH_2\mathit{CH_3}$	t, 7	1.26	1.20	1.17	1.20	1.24	1.24
L-ethyl lactate	▼	CH	q, 6.9	4.30-4.22, m	4.24-4.09, m	4.14-4.08, m	4.21-4.11, m	4.22	4.40
		CH_2	q, 7.1	4.25	4.24-4.09, m	4.08	4.21-4.11, m	4.18	4.23
		OH	d, 5.5	2.79	-	5.35	3.33	-	-
		$\mathit{CH_3}CH$	d, 6.9	1.42	1.32	1.24	1.31	1.36	1.41
		$\mathit{CH_3}CH_2$	t, 7.1	1.31	1.23	1.19	1.23	1.27	1.28
ethylene glycol	▲	CH_2	s	3.76	3.58-3.54, m	3.40-3.38, m	3.52-3.50, m	3.59	3.67
		OH	m	2.28, br s	-	4.46-4.43	2.72-2.69	-	-

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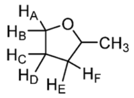
Table 1. continued

		proton	mult, *J*	$CDCl_3$	acetone-d_6	DMSO-d_6	CD_3CN	CD_3OD	D_2O
ethyl *tert*-butyl ether (ETBE)	▼	CH_2	q, 7.0	3.41	3.37	3.33	3.38	3.45	3.54
		$(CH_3)_3$	s	1.20	1.14	1.12	1.14	1.19	1.23
		CH_3	t, 7.0	1.17	1.06	1.04	1.07	1.13	1.15
formic acid	▼	HCO	s	8.03	8.11	8.14	8.03	8.07	8.26
glycol diacetate	▲	CH_2	s	4.27	4.24	4.19	4.21	4.25	4.34
		CH_3	s	2.09	2.01	2.02	2.01	2.04	2.12
n-heptane	▼	CH_2	m	1.32-1.24	1.33-1.25	1.30-1.22	1.33-1.25	1.34-1.24	1.33-1.23
		CH_3	t, 6.8	0.88	0.88	0.86	0.89	0.90	0.87
iso-propanol	▲	CH	septd, 6.1, 4.3	4.03, sept (6.1)	3.95-3.84, m[f]	3.77	3.86	3.92, sept (6.1)	4.02, sept (6.2)
		CH_3	d, 6.1	1.21	1.10 [1.10][c]	1.04	1.09	1.15	1.18
		OH	d, 4.3	-	3.39	4.34	2.51	-	-
iso-propyl acetate	▲	CH	sept, 6.3	4.99	4.91	4.86	4.91	4.95	4.98
		CH_3CO	s	2.02	1.94	1.96	1.94	1.99	2.07
		$(CH_3)_2$	d, 6.3	1.23	1.19	1.17	1.19	1.22	1.25
methanol	▲	CH_3	d, 5.3	3.49, s	3.31 [3.30][c, g]	3.17	3.28	3.34, s	3.36, s
		OH	q, 5.3	1.05, br s	3.12	4.10	2.17	-	-
methyl acetate	▲	OCH_3	s	3.67	3.59	3.57	3.60	3.64	3.69
		CH_3CO	s	2.06	1.98	2.00	1.99	2.02	2.09
methyl cyclohexane	▼	CH_2	m	1.70-1.60	1.70-1.59	1.67-1.57	1.71-1.59	1.72-1.61	-
		CH_2, CH	m	1.39-1.06	1.39-1.07	1.38-1.03	1.40-1.08	1.40-1.09	-
		CH_2	m	0.92-0.82	0.93-0.83	0.91-0.81	0.94-0.84	0.94-0.84	-
		CH_3	d, 6.6	0.86	0.85	0.84	0.86	0.87	-
methyl ethyl ketone[a]	▲	CH_3CO	s	2.14	2.07	2.07	2.06	2.12	2.19
		CH_2	q, 7	2.46	2.45	2.43	2.43	2.50	3.18
		$CH_2\mathit{CH_3}$	t, 7	1.06	0.96	0.91	0.96	1.01	1.26
methyl *iso*-butyl ketone	▲	CH_2	d, 7.0	2.30	2.31	2.30	2.29	2.35	2.43
		CH	nonet, 6.8	2.13	2.12-2.02, m	1.99	2.08-2.02, m	2.09	2.08
		CH_3CO	s	2.12	2.06	2.06	2.05	2.11	2.21
		$(CH_3)_2$	d, 6.7	0.92	0.88	0.85	0.88	0.91	0.90
methyl *tert*-butyl ether (MTBE) [a]	▼	OCH_3	s	3.22	3.13	3.08	3.13	3.20	3.22
		CCH_3	s	1.19	1.13	1.11	1.14	1.15	1.21
2-methyl tetrahydrofuran	▼	CH	dp, 7.9, 6.1	3.94	3.83	3.82	3.85	3.95	4.03
		$OC\mathit{H_A}H_B$	td, 7.7, 5.9	3.89	3.78	3.75	3.79	3.86	3.88
		$OCH_A\mathit{H_B}$	td, 8.0, 6.3	3.71	3.58	3.55	3.60	3.70	3.74
		H_c, H_D, H_E	m	2.03-1.81	2.00-1.75	1.97-1.72	2.00-1.76	2.06-1.85	2.11-1.86
		H_F	ddt, 11.7, 8.8, 7.6	1.41	1.34	1.31	1.35	1.42, dq (11.6, 8.0)	1.47, dq (12.0, 8.2)
		CH_3	d, 6.1	1.23	1.14	1.12	1.15	1.20	1.23
pyridine	▼	CH (2,6)	m	8.62-8.61	8.59-8.57	8.59-8.57	8.58-8.56	8.54-8.52	8.54-8.52
		CH (4)	tt, 7.6, 1.8	7.68	7.76	7.79	7.73	7.85	7.91-7.86, m
		CH (3,5)	m	7.30-7.26	7.36-7.33	7.40-7.37	7.34-7.31	7.45-7.42	7.48-7.45
sulfolane	▲	CH_2SO_2	m	3.05-3.02	2.97-2.93	3.01-2.97	2.96-2.92	3.03-2.99	3.19-3.15
		CH_2	m	2.25-2.21	2.21-2.17	2.09-2.05	2.16-2.12	2.21-2.18	2.26-2.22
tert-amyl methyl ether (TAME)	▼	OCH_3	s	3.18	3.10	3.05	3.10	3.17	3.20
		CH_2	q, 7.5	1.49	1.46	1.42	1.46	1.51	1.55
		$(CH_3)_2$	s	1.13	1.07	1.05	1.08	1.13	1.17
		$CH_2\mathit{CH_3}$	t, 7.5	0.87	0.82	0.79	0.83	0.86	0.85
tetrahydrofuran [a]	▼	CH_2O	m	3.76-3.73	3.64-3.61	3.62-3.59	3.66-3.63	3.74-3.71	3.78-3.74
		CH_2	m	1.87-1.84	1.81-1.77	1.78-1.75	1.82-1.79	1.88-1.85	1.91-1.88
toluene [a]	▼	CH (3,5)	m	7.28-7.24	7.26-7.22	7.27-7.23	7.27-7.23	7.23-7.19	7.36-7.33
		CH (2,4,6)	m	7.18-7.14	7.18-7.12	7.19-7.13	7.20-7.13	7.16-7.09	7.29-7.22
		CH_3	s	2.36	2.31	2.30	2.33	2.32	2.35
xylenes	▼								
o-xylene		CH	m	7.14-7.08	7.12-7.03	7.14-7.04	7.15-7.05	7.10-7.01	-
		CH_3	s	2.26	2.23	2.21	2.25	2.24	-
m-xylene		CH (5)	t, 7.5	7.15	7.11	7.13	7.13	7.08	7.24
		CH (2,4,6)	m	7.00-6.96	6.99-6.94	6.99-6.95	7.01-6.96	6.97-6.92	7.14-7.07
		CH_3	s	2.32	2.27	2.26	2.28	2.27	2.31
p-xylene		CH	s	7.06	7.05	7.05	7.06	7.02	7.18
		CH_3	s	2.31	2.26	2.24	2.27	2.26	2.30
ethyl benzene		CH (3,5)	m	7.30-7.26	7.29-7.25	7.29-7.26	7.30-7.25	7.26-7.22	-
		CH (2,6)	m	7.23-7.15	7.22-7.19	7.22-7.14	7.23-7.21	7.18-7.16	-
		CH (4)	m	7.23-7.15	7.17-7.13	7.22-7.14	7.19-7.14	7.14-7.10	-
		CH_2	q, 7.6	2.65	2.63	2.60	2.63	2.62	-
		CH_3	t, 7.6	1.24	1.20	1.17	1.21	1.21	-

[a] Data for these solvents are from refs 7 and 8. Green triangles = Rated as "recommended" in CHEM21 solvent selection guides. Yellow, upside down triangles = Rated as "problematic" in CHEM21 solvent selection guides (see refs 6 and 9). [b] Chemical shifts not determined due to reactivity in deuterated solvent. [c] Chemical shifts in brackets correspond to −OD isotopomer. See text for more information. [d] A second set of resonances was observed for anisole in D_2O: 6.79, t (7.9); 6.50−6.43, m; 3.08, s. See text and Supporting Information for more information. [e] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone. [f] Overlapping −OH and −OD isotopomer resonances were observed. [g] 1:1:1 triplet, J_{H-D} = 0.8 Hz.

and spectral similarity. Standard solutions were prepared using weighed amounts of the following compounds: *o*-xylene/*iso*-amyl alcohol; *m*-xylene/*iso*-butyl acetate; *p*-xylene/*iso*-propyl acetate; *p*-cymene/*n*-butyl acetate; toluene/*n*-butyl alcohol; anisole/*iso*-butyl alcohol; pyridine/methyl *iso*-butyl ketone; ethylbenzene/acetic anhydride; formic acid/*iso*-amyl acetate;

Table 2. ^{13}C NMR Data

			$CDCl_3$	acetone-d_6	DMSO-d_6	CD_3CN	CD_3OD	D_2O
solvent residual peak			77.06±0.03	29.82±0.01 206.03±0.10	39.53±0.05	1.32±0.01 118.26±0.03	49.03±0.01	
acetic acid [a]	▲	CO	175.99	172.31	171.93	173.21	175.11	177.21
		$\mathrm{CH_3}$	20.81	20.51	20.95	20.73	20.56	21.03
acetic anhydride	▲	CO	166.38	167.44	166.89	168.02	-[b]	-[b]
		$\mathrm{CH_3}$	22.15	22.05	21.90	22.45	-[b]	-[b]
acetone [a]	▲	CO	207.07	205.87	206.31	207.43	209.67	215.94
		$\mathrm{CH_3}$	30.92	30.60	30.56	30.91	30.67	30.89
acetonitrile [a]	▼	CN	116.43	117.60	117.91	118.26	118.06	119.68
		$\mathrm{CH_3}$	1.89	1.12	1.03	1.79	0.85	1.47
iso-amyl acetate	▲	CO	172.15	171.02	170.28	171.91	173.08	-
		$\mathrm{OCH_2}$	63.56	63.23	62.18	63.71	64.22	-
		$C\mathrm{H_2CH}$	37.29	38.18	36.83	38.16	38.53	-
		CH	25.09	25.77	24.47	25.90	26.27	-
		$\mathrm{(CH_3)_2}$	22.45	22.71	22.20	22.74	22.82	-
		$C\mathrm{H_3CO}$	21.05	20.80	20.64	21.17	20.87	-
iso-amyl alcohol	▲	$\mathrm{CH_2OH}$	61.36	60.72 [60.59][c]	58.91	60.94	61.28	60.82
		$C\mathrm{H_2CH}$	41.79	42.80 [42.75][c]	41.54	42.66	42.70	40.96
		CH	24.74	25.43	24.18	25.56	25.86	24.65
		$\mathrm{CH_3}$	22.62	22.98	22.52	22.96	23.02	22.39
anisole	▲	C (1)	159.59	160.71	159.30	160.74	161.15	-
		CH (3,5)	129.44	130.21	129.40	130.48	130.41	-
		CH (4)	120.67	121.25	120.41	121.52	121.59	-
		CH (2,6)	113.93	114.68	113.87	114.85	114.91	-
		$\mathrm{CH_3}$	55.14	55.34	54.87	55.76	55.56	-
benzyl alcohol	▲	C (1)	140.98	143.42 [143.39][c]	142.44	143.17	142.74	140.84
		CH (3,5)	128.54	128.92	127.92	129.26	129.37	129.34
		CH (4)	127.61	127.55	126.50	127.97	128.28	128.43
		CH (2,6)	126.98	127.35	126.31	127.69	128.01	128.06
		$\mathrm{CH_2}$	65.31	64.68 [64.55][c]	62.82	64.79	65.28	64.51
n-butanol	▲	$\mathrm{CH_2OH}$	62.76	62.15 [62.01][c]	60.31	62.35	62.71	62.17
		$C\mathrm{H_2CH_2OH}$	34.91	35.93 [35.88][c]	34.63	35.80	35.84	34.06
		$C\mathrm{H_2CH_3}$	18.92	19.72	18.56	19.80	20.04	18.97
		$\mathrm{CH_3}$	13.86	14.20	13.75	14.24	14.24	13.66
iso-butanol	▲	$\mathrm{CH_2}$	69.80	69.46 [69.33][c]	67.83	69.53	69.95	69.27
		CH	30.87	31.74 [31.71][c]	30.53	31.73	31.93	30.37
		$\mathrm{CH_3}$	18.86	19.36	19.09	19.32	19.38	18.83
tert-butanol [a]	▲	C	69.15	68.16 [68.03][c]	66.88	68.74	69.40	70.36
		$\mathrm{CH_3}$	31.25	31.61 [31.57][c]	30.38	30.68	30.91	30.29
n-butyl acetate [d]	▲	CO	171.20	170.94	170.27	171.73	173.04	175.46
		$\mathrm{OCH_2}$	64.36	64.44	63.40	64.84	65.44	66.12
		$\mathrm{OCH_2}C\mathrm{H_2}$	30.70	31.50	30.12	31.52	31.84	30.46
		$C\mathrm{H_3CO}$	20.99	20.76	20.60	21.12	20.83	21.06
		$C\mathrm{H_2CH_3}$	19.16	19.77	18.54	19.87	20.18	19.07
		$\mathrm{CH_2}C\mathrm{H_3}$	13.71	13.94	13.44	14.02	14.03	13.51
iso-butyl acetate	▲	CO	171.19	170.89	170.28	171.71	173.00	175.52
		$\mathrm{CH_2}$	70.63	70.71	69.61	71.02	71.73	72.22
		CH	27.71	28.49	27.16	28.61	28.95	27.70
		$C\mathrm{H_3CO}$	20.93	20.69	20.57	21.05	20.76	20.99
		$\mathrm{(CH_3)_2}$	19.08	19.26	18.79	19.29	19.36	18.77
chlorobenzene	▼	C (1)	134.29	134.63	133.00	134.74	135.31	-
		CH (3,5)	129.71	130.94	130.20	131.10	131.00	-
		CH (2,6)	128.62	129.30	128.30	129.45	129.56	-
		CH (4)	126.43	127.65	126.92	127.83	127.73	-
cyclohexane [a]	▼	$\mathrm{CH_2}$	26.94	27.51	26.33	27.63	27.96	-
cyclohexanone [a]	▲	CO	212.57	210.36	210.63	211.99	214.69	221.22
		$\mathrm{CH_2}$ (2,6)	41.97	42.24	41.32	42.44	42.61	42.02
		$\mathrm{CH_2}$ (3,5)	27.00	27.68	26.46	27.80	28.16	27.50
		$\mathrm{CH_2}$ (4)	24.97	25.59	24.32	25.62	25.86	24.77
cyclopentyl methyl ether (CPME)	▼	CH	83.03	83.35	81.92	83.62	84.47	84.40
		$\mathrm{CH_3}$	56.30	56.18	55.47	56.38	56.55	56.04
		$\mathrm{CH_2}$ (2,5)	31.97	32.51	31.35	32.63	32.85	31.87
		$\mathrm{CH_2}$ (3,4)	23.55	24.14	23.05	24.28	24.45	23.61
p-cymene (4-*iso*-propyltoluene)[d]	▼	C (4)	145.89	146.54	145.22	146.91	146.99	-
		C (1)	135.14	135.70	134.46	136.16	136.15	-
		CH (2,6)	128.98	129.71	128.72	129.91	129.90	-
		CH (3,5)	126.28	126.99	125.98	127.23	127.19	-
		$C\mathrm{H(CH_3)_2}$	33.70	34.40	32.92	34.48	34.98	-
		$\mathrm{(CH_3)_2}$	24.10	24.40	23.89	24.41	24.55	-
		$\mathrm{Ar{-}CH_3}$	20.95	20.94	20.48	21.00	21.03	-

Table 2. continued

			$CDCl_3$	acetone-d_6	DMSO-d_6	CD_3CN	CD_3OD	D_2O
dichloromethane [a]	▼	CH_2	53.52	54.95	54.84	55.32	54.78	-
dimethyl carbonate [a]	▲	CO	156.45	157.04	155.76	157.26	157.91	163.96
		CH_3	54.89	54.95	54.63	55.39	55.25	55.81
dimethyl sulfoxide [a]	▼	CH_3	40.76	41.23	40.45	41.31	40.45	39.39
DMPU [d,e]	▼	CO	156.85	156.97	155.89	157.54	158.90	158.99
		NCH_2	47.93	48.57	47.31	48.69	48.92	48.24
		CH_3	35.67	35.60	35.11	35.81	35.96	35.91
		CH_2	22.24	23.13	21.76	23.10	23.04	21.80
ethanol [a]	▲	CH_2	58.28	57.76 [57.72][c]	56.07	57.96	58.26	58.05
		CH_3	18.41	18.87 [18.82][c]	18.51	18.80	18.40	17.47
ethyl acetate [a]	▲	CO	171.36	170.96	170.31	171.68	172.89	175.26
		CH_2	60.49	60.56	59.74	60.98	61.50	62.32
		CH_3CO	21.04	20.83	20.68	21.16	20.88	21.15
		CH_2CH_3	14.19	14.50	14.40	14.54	14.49	13.92
L-ethyl lactate	▼	CO	175.70	175.57 [175.54][c]	174.49	175.96	176.41	177.14
		CH	66.78	67.43 [67.32][c]	65.91	67.57	67.90	67.37
		CH_2	61.63	61.17	59.90	61.74	61.98	62.84
		CH_3CH	20.41	20.78 [20.72][c]	20.30	20.77	20.59	19.80
		CH_3CH_2	14.18	14.48	14.04	14.52	14.52	13.91
ethylene glycol [a]	▲	CH_2	63.79	64.28 [64.15][c]	62.76	64.22	64.30	63.17
ethyl *tert*-butyl ether (ETBE)	▼	C	72.56	72.57	71.88	72.95	74.13	75.28
		CH_2	56.79	57.06	56.03	57.32	57.95	57.88
		$(CH_3)_3$	27.64	27.86	27.39	27.89	27.86	27.16
		CH_3	16.35	16.66	16.17	16.72	16.47	15.66
formic acid	▼	CO	165.40	162.29	162.86	162.57	164.41	166.31
glycol diacetate	▲	CO	170.76	170.84	170.15	171.52	172.55	174.71
		CH_2	62.21	62.81	61.85	63.04	63.48	63.42
		CH_3	20.80	20.63	20.51	20.98	20.65	20.84
n-heptane	▼	CH_2 (3,5)	31.91	32.61	31.17	32.67	33.06	-
		CH_2 (4)	29.04	29.74	28.27	29.80	30.17	-
		CH_2 (2,6)	22.71	23.33	22.00	23.45	23.75	-
		CH_3	14.11	14.33	13.84	14.41	14.44	-
iso-propanol [a]	▲	CH	64.50	63.74 [63.60][c]	64.92	64.30	64.71	64.88
		CH_3	25.14	25.77 [25.72][c]	25.43	25.55	25.27	24.38
iso-propyl acetate	▲	CO	170.63	170.38	169.72	171.16	172.52	174.77
		CH	67.64	67.74	66.89	68.23	69.08	70.28
		$(CH_3)_2$	21.84	22.00	21.53	22.06	22.03	21.44
		CH_3CO	21.42	21.19	21.00	21.55	21.28	21.53
methanol [a]	▲	CH_3	50.41	49.81 [49.66][c]	48.59	49.90	49.86	49.50
methyl acetate	▲	CO	171.48	171.29	170.73	172.08	173.21	175.64
		OCH_3	51.58	51.51	51.17	51.97	52.04	52.77
		CH_3CO	20.67	20.45	20.40	20.81	20.50	20.73
methyl cyclohexane	▼	CH_2CH	35.51	36.12	34.96	36.19	36.58	-
		CH	32.79	33.47	32.20	33.56	33.99	-
		CH_2	26.50	27.09	25.91	27.21	27.52	-
		CH_2	26.40	26.97	25.86	27.09	27.40	-
		CH_3	22.91	23.16	22.71	23.22	23.30	-
methyl ethyl ketone [a]	▲	CO	209.56	208.30	208.72	209.88	212.16	218.43
		CH_2	36.89	36.75	35.83	37.09	37.34	37.27
		CH_3CO	29.49	29.30	29.26	29.60	29.39	29.49
		CH_2CH_3	7.86	8.03	7.61	7.14	8.09	7.87
methyl *iso*-butyl ketone	▲	CO	208.83	207.75	208.02	209.34	211.70	218.10
		CH_2	52.82	52.80	51.74	53.04	53.41	52.96
		CH_3CO	30.34	30.15	29.98	30.43	30.27	30.24
		CH	24.66	25.05	23.83	25.28	25.70	25.13
		$(CH_3)_2$	22.55	22.73	22.23	22.75	22.82	22.26
methyl *tert*-butyl ether (MTBE) [a]	▼	C	72.87	72.81	72.04	73.17	74.32	75.62
		OCH_3	49.45	49.35	48.70	49.52	49.66	49.37
		CCH_3	26.99	27.24	26.79	27.28	27.22	26.60
2-methyl tetrahydrofuran	▼	CH	75.23	75.50	74.21	75.78	76.75	76.81
		CH_2O	67.72	67.87	66.65	68.10	68.68	68.13
		CH_2CH	33.11	33.80	32.62	33.85	34.05	32.93
		CH_2CH_2O	25.92	26.47	25.32	26.59	26.77	25.77
		CH_3	20.97	21.29	20.81	21.34	21.14	20.34
pyridine	▼	CH (2,6)	149.90	150.67	149.54	150.78	150.12	149.16
		CH (4)	135.89	136.57	136.01	136.91	138.38	138.21
		CH (3,5)	123.71	124.54	123.80	124.77	125.56	125.04
sulfolane	▲	CH_2SO_2	51.16	51.60	50.51	51.86	52.04	51.58
		CH_2	22.79	23.31	22.07	23.38	23.68	22.84

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Table 2. continued

			$CDCl_3$	acetone-d_6	DMSO-d_6	CD_3CN	CD_3OD	D_2O
tert-amyl methyl ether (TAME)	▼	C	74.77	74.73	73.85	75.16	76.46	77.73
		OCH_3	49.04	48.96	48.29	49.16	49.32	48.92
		CH_2	32.14	32.91	31.65	32.90	32.99	31.69
		$(CH_3)_2$	24.50	24.73	24.20	24.83	24.83	24.24
		CH_2CH_3	8.22	8.40	8.00	8.53	8.47	8.14
tetrahydrofuran [a]	▼	CH_2O	68.00	68.07	67.07	68.32	68.82	68.45
		CH_2	25.68	26.19	25.19	26.30	26.50	25.63
toluene [a]	▼	C (1)	137.88	138.49	137.26	138.94	138.93	-
		CH (2,6)	129.05	129.75	128.81	129.95	129.94	-
		CH (3,5)	128.24	129.03	128.11	129.25	129.23	-
		CH(4)	125.31	126.11	125.22	126.29	126.32	-
		CH_3	21.45	21.41	20.95	21.50	21.51	-
xylenes	▼							
o-xylene		C (1,2)	136.49	137.03	135.91	137.51	137.37	-
		CH (3,6)	129.59	130.28	129.29	130.46	130.47	-
		CH (4,5)	125.79	126.58	125.61	126.78	126.81	-
		CH_3	19.71	19.68	19.24	19.79	19.77	-
m-xylene [d]		C (1,3)	137.78	138.34	137.07	138.80	138.79	-
		CH (2)	129.91	130.52	129.51	130.71	130.70	-
		CH (5)	128.15	128.93	127.98	129.16	129.13	-
		CH (4,6)	126.04	126.78	125.83	126.95	126.99	-
		CH_3	21.33	21.32	20.83	21.40	21.42	-
p-xylene		C (1,4)	134.67	135.27	134.03	135.68	135.71	-
		CH (2,3,5,6)	128.92	129.65	128.69	129.85	129.84	-
		CH_3	20.94	20.94	20.49	21.00	21.02	-
ethylbenzene		C (1)	144.25	144.99	143.65	145.42	145.48	-
		CH (3,5)	128.31	129.12	128.18	129.34	129.33	-
		CH (2,6)	127.85	128.59	127.63	128.81	128.80	-
		CH (4)	125.58	126.40	125.50	126.59	126.62	-
		CH_2	28.89	29.43	28.11	29.50	29.89	-
		CH_3	15.60	16.08	15.55	16.17	16.25	-

[a] Data for these solvents are from refs 7 and 8. Green triangles = Rated as "recommended" in CHEM21 solvent selection guides. Yellow, upside down triangles = Rated as "problematic" in CHEM21 solvent selection guides (see refs 6 and 9). [b] Chemical shifts not determined due to reactivity in deuterated solvent. [c] Chemical shifts in brackets correspond to −OD isotopomer. See text for more information. [d] Solvent was analyzed individually, not in pairs. [e] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

DMPU/*n*-heptane; tetrahydrofuran/methylcyclohexane; ethyl *tert*-butyl ether/methyl acetate; glycol diacetate/*tert*-amyl methyl ether; cyclopentyl methyl ether/benzyl alcohol; *L*-ethyl lactate/sulfolane; 2-methyl-tetrahydrofuran/chlorobenzene. When necessary, assignments were confirmed by gHSQC and HMBC experiments or analyzed individually.

^1H NMR samples were prepared with 3 μL of the standard solution and 600 μL of deuterated solvent and were referenced to TMS (0 ppm). $^{13}C\{^1H\}$ NMR samples were prepared using 25 μL of stock solution and 600 μL of deuterated solvent and referenced to TMS (0 ppm). In the original publication, ^1H NMR chemical shifts in D_2O were reported relative to sodium 3-(trimethylsilyl)propanesulfonate. To minimize spectral overlap of the reference standard with resonances of interest, the commercially available sodium salt of 3-(trimethylsilyl)-propionic-2,2,3,3-d_4 acid (TSP) was instead used as a chemical shift reference (0 ppm). The ^1H NMR singlet for the -$SiMe_3$ groups of TSP and sodium 3-(trimethylsilyl)propanesulfonate were within ±0.02 ppm.[10] For ^{13}C NMR spectra in D_2O, 5 μL of methanol was added to each corresponding NMR sample, and its methyl resonance was set to 49.50 ppm.

■ RESULTS AND DISCUSSION

^1H NMR spectral data for industrially preferred solvents in six commonly used NMR solvents ($CDCl_3$, DMSO-d_6, CD_3CN, acetone-d_6, CD_3OD and D_2O) are provided in Table 1. Solvents in Table 1 were classified as either recommended (green triangles) or problematic (yellow, upside down triangles) in the initial CHEM21 survey.[6] Problematic solvents pose hazards that can typically be managed in a production environment. Solvents that were rated as hazardous were excluded. Additionally, less-classical solvents (e.g., *p*-cymene, *L*-ethyl lactate) that scored better than a 7 in both health and environmental categories from the second communication published by CHEM21 were included.[9] Although NMR data for 19 of these solvents were included in either the original report or the 2010 update,[7,8] data for an additional 29 solvents were obtained. Furthermore, data for previously reported solvents have been modified to include chemical shift ranges of multiplets. Table 2 contains $^{13}C\{^1H\}$ NMR data for these same solvent impurities. A tabulation of the ^1H and ^{13}C NMR data for all 48 impurities in order of chemical shift is included in the Supporting Information to aid in the assignment of unknown peaks.

All of the compounds in Table 1 were obtained as single isomers. However, some solvents used in manufacturing processes are often obtained as mixtures of components that are isolated by distillation over a boiling point range. For example, xylenes is often comprised of a mixture of the *ortho*, *meta*, and *para* isomers, along with ethylbenzene. NMR data for each individual component of xylenes are provided to aid in the identification of all residual solvent impurities that could be encountered when xylenes is used.

Alcohols are commonly preferred solvents that are often available from renewable sources. An often overlooked spectral feature of alcohols is that occasionally a second set of certain resonances can be observed due to slow exchange between ROH and ROD isotopomers on the NMR time scale.[11] This is manifested in a small, isotopically induced chemical shift that can be observed in both ^{1}H and ^{13}C NMR spectra. We found the −OD isotopomer to be more abundant in acetone-d_6 that contained trace H_2O and HOD. Use of anhydrous acetone-d_6 minimized the formation of the −OD isotopomer and simplified spectra. This second set of resonances is especially noticeable in ^{13}C NMR spectra of alcohols in acetone-d_6, and distinct ^{13}C NMR resonances are observed for carbons α- and β- to the alcohol moiety. ^{1}H NMR spectra of alcohols in acetone-d_6 typically show an −OH resonance that has a lower integration due to partial incorporation of deuterium. Overlap of the −C*H*OH and −C*H*OD resonances is typically observed. Chemical shifts for the minor isotopomer are shown parenthetically for alcohols in Tables 1 and 2 (MeOH, EtOH, *iso*-PrOH, *n*-BuOH, *iso*-BuOH, *t*-BuOH, *iso*-AmOH, benzyl alcohol, ethyl *L*-lactate, and ethylene glycol). In other solvents (DMSO-d_6, CD_3CN), exchange with residual H_2O can be slow on the NMR time scale, and *J*-coupling between the −O*H* and −C*H*(R)OH protons can frequently be observed. ^{1}H NMR data for the alcohols in Table 1 denote the observed multiplicity due to this coupling.

One additional spectral feature deserves mention since it could be otherwise misinterpreted. ^{1}H NMR spectra of anisole in D_2O exhibited two sets of resonances (Supporting Information). Spectra taken in other solvents were unremarkable. This phenomenon may be related to the relatively low solubility of anisole in D_2O. Unusual interactions between anisole and D_2O have been previously attributed to isotopically induced, hydrogen bond conformational differences and to the formation of π-stacked dimers.[12]

In conclusion, solvent selection is an important criterion for the development of sustainable chemical processes. The data provided in Tables 1 and 2 should simplify the identification of trace impurities in the NMR spectra of research samples resulting from the use of industrially preferred solvents in synthesis and workup procedures. It is our hope that these data will serve as a practical resource that facilitates the adoption of safer, greener, and more sustainable solvents throughout the chemical industry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00417.

> Tables of ^{1}H and ^{13}C NMR multiplets in order of decreasing order of chemical shift in $CDCl_3$, acetone-d_6, DMSO-d_6, CD_3CN, CD_3OD, and D_2O. ^{1}H NMR spectrum of anisole in D_2O (PDF)

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Notes

The authors declare no competing financial interest.

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